

=> fil hcap

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FILE COVERS 1907 - 27 Nov 2004 VOL 141 ISS 23
FILE LAST UPDATED: 26 Nov 2004 (20041126/ED)

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=> fil medlin

FILE 'MEDLINE' ENTERED AT 12:01:56 ON 27 NOV 2004

FILE LAST UPDATED: 26 NOV 2004 (20041126/UP). FILE COVERS 1950 TO DATE.

On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD for details.

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See <http://www.nlm.nih.gov/mesh/> and http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description of changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil biosis

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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 24 November 2004 (20041124/ED)

FILE RELOADED: 19 October 2003.

=> fil jicst

FILE 'JICST-EPLUS' ENTERED AT 12:02:02 ON 27 NOV 2004
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=> fil pascal

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FILE LAST UPDATED: 22 NOV 2004 <20041122/UP>
FILE COVERS 1977 TO DATE.

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=> fil caba

FILE 'CABA' ENTERED AT 12:02:10 ON 27 NOV 2004
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FILE COVERS 1973 TO 8 Nov 2004 (20041108/ED)

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The CABA file was reloaded 7 December 2003. Enter HELP RLOAD for details.

=> fil embase

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FILE COVERS 1974 TO 19 Nov 2004 (20041119/ED)

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=> fil confsci

FILE 'CONFSCI' ENTERED AT 12:02:18 ON 27 NOV 2004
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FILE COVERS 1973 TO 18 Nov 2004 (20041118/ED)

=> fil wpix

FILE 'WPIX' ENTERED AT 12:02:21 ON 27 NOV 2004
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FILE LAST UPDATED: 25 NOV 2004 <20041125/UP>
MOST RECENT DERWENT UPDATE: 200476 <200476/DW>

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=> file stnguide

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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Nov 19, 2004 (20041119/UP).

=> d que 111

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L4 (      6104)SEA FILE=HCAPLUS ABB=ON  PLU=ON  YAMASHITA, T?/AU
L5 (      206)SEA FILE=HCAPLUS ABB=ON  PLU=ON  NARA, H?/AU
L6 (      583)SEA FILE=HCAPLUS ABB=ON  PLU=ON  TAKIZAWA, M?/AU
L7 (     2162)SEA FILE=HCAPLUS ABB=ON  PLU=ON  YOSHIMURA, K?/AU
L8 (      49)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L4 OR L5 OR L6 OR L7) AND
      ?THIOL?
L9 (      5)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 AND ?PYRROL?
L10 (     10)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 AND ?TAKEDA?/CS,SO,PA
L11      11 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L9 OR L10
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(FILE 'MEDLINE, BIOSIS, JICST-EPLUS, PASCAL, CABA, EMBASE, CONFSCI, WPIX'
ENTERED AT 11:52:23 ON 27 NOV 2004)

=> d que 162

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L53      17677 SEA YAMASHITA, T?/AU
L54      479 SEA NARA, H?/AU
L55     1745 SEA TAKIZAWA, M?/AU
L56     6636 SEA YOSHIMURA, K?/AU
L57    64888 SEA METALLOPROTEAS? OR ?METALLOPROTEAS? OR MMP?
L58      63 SEA (L53 OR L54 OR L55 OR L56) AND L57
L59     31 DUP REM L58 (32 DUPLICATES REMOVED)
L60      7 SEA L59 AND (?THIO? OR THIO?)
L61     10 SEA L59 AND (?TAKEDA? OR TAKEDA?)/SO,CS,PA
L62     12 SEA L60 OR L61
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=> dup rem l11 l62

FILE 'HCAPLUS' ENTERED AT 12:03:08 ON 27 NOV 2004
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 PROCESSING COMPLETED FOR L11
 PROCESSING COMPLETED FOR L62

L63 20 DUP REM L11 L62 (3 DUPLICATES REMOVED)
 ANSWERS '1-11' FROM FILE HCAPLUS
 ANSWERS '12-13' FROM FILE MEDLINE
 ANSWER '14' FROM FILE BIOSIS
 ANSWER '15' FROM FILE EMBASE
 ANSWERS '16-20' FROM FILE WPIX

=> d ibib abs ed

L63 ANSWER 1 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
 ACCESSION NUMBER: 2003:875277 HCAPLUS
 DOCUMENT NUMBER: 139:364833
 TITLE: Preparation of heterocyclic thiol compounds
 as matrix metalloprotease inhibitors
 INVENTOR(S): Kajino, Masahiro; Takizawa, Masayuki;
 Notoya, Kohei; Nara, Hiroshi; Ikemoto,
 Tomomi; Nishiguchi, Atsuko
 PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
 SOURCE: PCT Int. Appl., 116 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003091242	A1	20031106	WO 2003-JP5255	20030424
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
JP 2004002405	A2	20040108	JP 2003-119405	20030424

PRIORITY APPLN. INFO.:

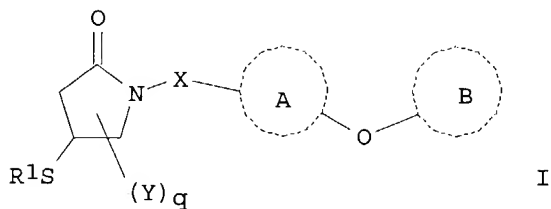
JP 2002-126943

A 20020426

OTHER SOURCE(S):

MARPAT 139:364833

GI



AB The title compds. I [wherein the ring A is a substituted or unsubstituted aromatic heterocycle; the ring B is a substituted or unsubstituted homocycle or heterocycle; R1 is a hydrogen atom, a substituted or unsubstituted hydrocarbon group, an acyl group, a substituted or unsubstituted heterocyclic group or SR2 (R2 is a hydrogen atom, a substituted or unsubstituted hydrocarbon group, an acyl group or a substituted or unsubstituted heterocyclic group); X is a substituted or unsubstituted divalent C1-3 aliphatic hydrocarbon group; Y is a substituted or unsubstituted hydrocarbon group, a halogen atom, a carboxyl group, an acyl group, a substituted or unsubstituted hydroxyl group, a substituted or unsubstituted amino group, SR3 (R3 is a hydrogen atom, a substituted or unsubstituted hydrocarbon group, an acyl group or a substituted or unsubstituted heterocyclic group), an oxo group, a thioxo group, a substituted or unsubstituted imino group, a nitro group or a cyano group; and q is an integer of 0 to 5] are prepared. Processes for preparing I are disclosed. One compound of this invention at 1.5 nM gave 67% inhibition of MMP-13. Formulations are given.

ED Entered STN: 07 Nov 2003

REFERENCE COUNT:

8

THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs ed 2-

YOU HAVE REQUESTED DATA FROM 19 ANSWERS - CONTINUE? Y/(N):y

L63 ANSWER 2 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2002:888746 HCAPLUS

DOCUMENT NUMBER: 138:4599

TITLE: Preparation of fused imidazolidine derivatives as inhibitors of cartilage matrix degradation

INVENTOR(S): Funabashi, Yasunori; **Takizawa, Masayuki**; Morimoto, Shinji; Notoya, Kohei

PATENT ASSIGNEE(S): **Takeda Chemical Industries, Ltd., Japan**

SOURCE: PCT Int. Appl., 940 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002092606	A1	20021121	WO 2002-JP4640	20020514
WO 2002092606	C1	20021219		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
 GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS,
 LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,
 PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
 UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
 CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

JP 2003034691

A2

20030207

JP 2002-139642

20020515

PRIORITY APPLN. INFO.:

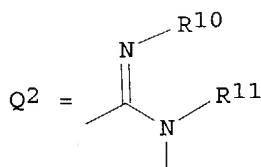
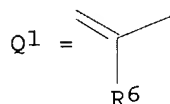
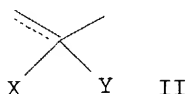
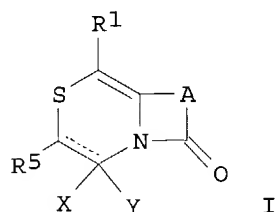
JP 2001-144608

A 20010515

OTHER SOURCE(S):

MARPAT 138:4599

GI



AB The title compds. I [R1 = (S)_nR2, etc.; n = 0 - 2; R2 = H, (un)substituted hydrocarbon, etc.; R5 = H, (un)substituted hydrocarbon, etc.; the moiety represented by II in I is Q1, etc.; R6 = H, (un)substituted hydrocarbon, etc.; A = Q2, etc.; R10 = H, ZR15, etc.; Z = SO2, etc.; R15 = (un)substituted hydrocarbon, etc.; R11 = H, (un)substituted hydrocarbon] are prepared. A process for preparing I is disclosed. Compds. of this invention in vitro at 0.1 μ M gave 20% to 55% inhibition of MMP-13 production. Formulations are given.

ED Entered STN: 22 Nov 2002

REFERENCE COUNT:

22

THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L63 ANSWER 3 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 2000:210116 HCAPLUS

DOCUMENT NUMBER: 132:251070

TITLE: Preparation and utilization of novel thiol derivatives

INVENTOR(S): Yamashita, Toshiro; Nara, Hiroshi; Takizawa, Masayuki; Yoshimura, Koji

PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan

SOURCE: PCT Int. Appl., 261 pp.

CODEN: PIXXD2

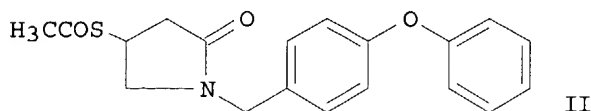
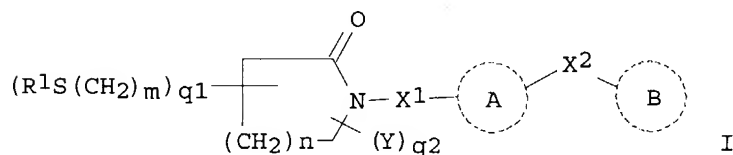
DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000017162	A1	20000330	WO 1999-JP5103	19990920
W: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2344412	AA	20000330	CA 1999-2344412	19990920
AU 9956537	A1	20000410	AU 1999-56537	19990920
JP 2000159747	A2	20000613	JP 1999-266295	19990920
EP 1132379	A1	20010912	EP 1999-943412	19990920
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6420415	B1	20020716	US 2001-787623	20010320
US 2003078253	A1	20030424	US 2002-161289	20020603
US 6699881	B2	20040302		
US 2004157894	A1	20040812	US 2004-757325	20040113
PRIORITY APPLN. INFO.:			JP 1998-266037	A 19980921
			WO 1999-JP5103	W 19990920
			US 2001-787623	A3 20010320
			US 2002-161289	A3 20020603
OTHER SOURCE(S):			MARPAT 132:251070	
GI				



AB Title compds [I; wherein the rings A and B represent each an optionally substituted homocycle or heterocycle, etc.; R1s are the same or different and each represents hydrogen, optionally substituted hydrocarbyl, acyl, etc.; X1 represents a bond, optionally substituted divalent aliphatic hydrocarbyl, etc.; X2 represents a bond, optionally substituted divalent aliphatic hydrocarbyl, O, etc.; Ys are the same or different and each represents hydrogen, optionally substituted hydrocarbyl, oxo, etc.; m is 0 or 1; n is an integer of 1 to 3; q1 is an integer of 1 to 2n+4; and q2 is an integer of 0 to 2n+3, provided that q1+q2 is 2n+4], stereoisomers, and salts thereof are prepared and tested as matrix metalloprotease inhibitors

and are useful as drugs. The title compound (R)-II was prepared and tested.
 ED Entered STN: 31 Mar 2000
 REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L63 ANSWER 4 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:747795 HCAPLUS

DOCUMENT NUMBER: 135:303882

TITLE: Preparation of thienobenzisoxazoles and
 thienoindazoles for prevention and treatment of bone
 or articular diseases

INVENTOR(S): Yasuma, Tsuneo; Mori, Akira; Kawase, Masahiro;
Takizawa, Masayuki; Miki, Shokyo; Takeda,
 Mitsuhiro

PATENT ASSIGNEE(S): **Takeda Chemical Industries, Ltd., Japan**

SOURCE: PCT Int. Appl., 486 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

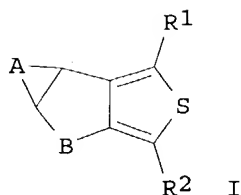
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

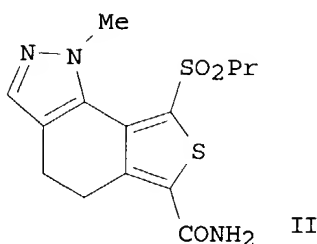
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001074823	A2	20011011	WO 2001-JP2614	20010329
WO 2001074823	A3	20020207		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
CA 2400858	AA	20011011	CA 2001-2400858	20010329
JP 2002255971	A2	20020911	JP 2001-94980	20010329
EP 1268486	A2	20030102	EP 2001-917582	20010329
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
US 2003158245	A1	20030821	US 2002-204472	20020821
PRIORITY APPLN. INFO.:			JP 2000-101373	A 20000331
			JP 2000-101374	A 20000331
			JP 2000-392843	A 20001225
			WO 2001-JP2614	W 20010329

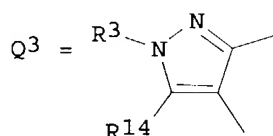
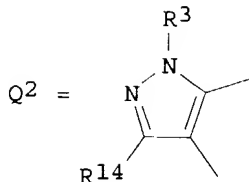
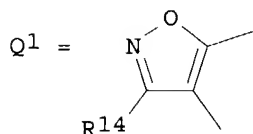
OTHER SOURCE(S): MARPAT 135:303882
 GI



I



II



AB The title fused thiophene derivs. I [wherein R1 = (un)substituted hydrocarbon, heterocyclic, sulfinyl, sulfonyl, hydroxyl, **thiol**, or amino; R2 = CN, CHO, CHS, etc.; ring A = Q1, Q2, or Q3; R3 = H or (un)substituted hydrocarbon, heterocyclic, hydroxyl, amino, sulfonyl, or acyl; R14 = H, halo, (un)substituted hydrocarbon or heterocyclic group, etc.; ring B = (un)substituted 5- to 7-membered hydrocarbon ring] and their intermediates were prepared using industrially advantageous processes as prophylactic and therapeutic drugs for bone or articular diseases. For example, cycloaddn. of MeNHNH2•H2O with 5-diethoxymethyl-3-propylsulfanyl-4-oxo-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxylic acid Et ester (preparation given) using HCl in EtOH (80%), followed by saponification (93%), amidation (79%), and oxidation with m-chloroperbenzoic acid (42%), gave II. The latter enhanced chondromodulin-I (ChM-I) mRNA expression in ATDC5, a substrain derived from mouse teratocarcinoma cell line AT805, with ChM-I band d. of 10-6 M.

ED Entered STN: 12 Oct 2001

L63 ANSWER 5 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:594557 HCAPLUS

DOCUMENT NUMBER: 127:220996

TITLE: Preparation of aziridine dicarboxylic acid derivatives as cathepsin L inhibitors

INVENTOR(S): Tsuboya, Shigetoshi; **Takizawa, Masayuki**; Hattori, Masahiko; Shirasaki, Mikio

PATENT ASSIGNEE(S): **Takeda Chemical Industries, Ltd., Japan**

SOURCE: Jpn. Kokai Tokkyo Koho, 22 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent

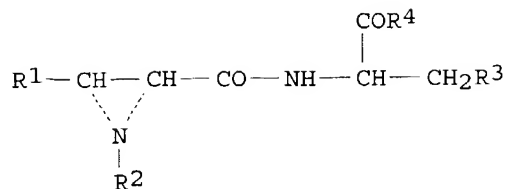
LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 09221470	A2	19970826	JP 1996-302886	19961114
PRIORITY APPLN. INFO.:			JP 1995-323374	19951212
OTHER SOURCE(S):	MARPAT	127:220996		

GI



I

AB The title compds. [I; R¹ = (Et esterified) carboxylyl; R² = H, Me, Et; R³ = Ph, naphthyl; R⁴ = MeO(CH₂)₃NH, Ph(CH₂)₂NH, etc.] are prepared I are useful as cathepsin L and **thiol** protease inhibitors and antiinflammatory agents for prevention and treatment of myocardopathy, osteoporosis and related bone diseases. Thus, aziridine derivative I (R¹ = EtO₂C, R² = H, R³ = Ph, R⁴ = NH(CH₂)₃OMe) (preparation given) was treated with aqueous NaOH in MeOH to give 87% I (R¹ = CO₂Na, R²-R⁴ = same as above), which showed IC₅₀ of 1.8 ng/mL against cathepsin L. A capsule formulation containing I was prepared

ED Entered STN: 17 Sep 1997

L63 ANSWER 6 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:210920 HCAPLUS

DOCUMENT NUMBER: 126:198634

TITLE: Interleukin inhibitor TAN-2178 and derivatives manufacture with Streptomyces

INVENTOR(S): Funahashi, Yasunori; Kawamura, Noriaki; Yoshimura, Koji; Makino, Haruhiko

PATENT ASSIGNEE(S): Takeda Chemical Industries Ltd, Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 32 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 09012595	A2	19970114	JP 1996-107404	19960426
PRIORITY APPLN. INFO.:			JP 1995-104458	19950427
OTHER SOURCE(S): MARPAT 126:198634				

AB Interleukin inhibitor TAN-2178 and derivs. R¹C(O)CH(CH₂R²)C(O)NHC(R³)C(O)C R⁵(CH₂R⁴)(CH₂R⁶) (I: R¹ = C₁-6 alkyl; R² and R⁴ = OH or substituted OH; R³ = 2-methylpropyl, etc.; R⁵ = OH; R⁶ = halogen, substituted **thiol** or **thiol**) are manufactured by culturing I-producing Streptomyces sp. AL-78099 and chemical synthesis. I inhibit the formation and/or biosynthesis of interleukin. Manufacture of TAN-2178 and 31 derivs. were shown. The physiol. and morphol. characteristics of Streptomyces sp. AL-78099 were also given.

ED Entered STN: 02 Apr 1997

L63 ANSWER 7 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1996:184020 HCAPLUS

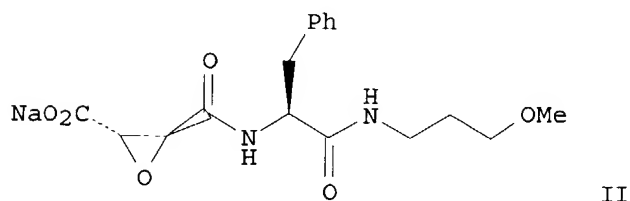
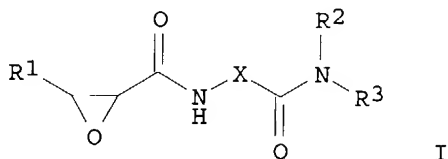
DOCUMENT NUMBER: 124:233141

TITLE: Epoxysuccinic acid peptide derivatives, their production, and use for treatment of bone disease and inhibition of **thiol** protease

INVENTOR(S): Tsubotani, Shigetoshi; Takizawa, Masayuki;

PATENT ASSIGNEE(S): Mizoguchi, Junji
 SOURCE: Takeda Chemical Industries, Ltd., Japan
 PCT Int. Appl., 65 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9532954	A1	19951207	WO 1995-JP1004	19950525
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, US, UZ, VN RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2190151	AA	19951207	CA 1995-2190151	19950525
AU 9525376	A1	19951221	AU 1995-25376	19950525
EP 763029	A1	19970319	EP 1995-919635	19950525
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 08104684	A2	19960423	JP 1995-132050	19950530
US 5679708	A	19971021	US 1995-513895	19950905
PRIORITY APPLN. INFO.:			JP 1994-119206	19940531
			JP 1994-186166	19940808
			WO 1995-JP1004	19950525
OTHER SOURCE(S):			MARPAT 124:233141	
GI				



AB The invention relates to compds. I [R1 = optionally esterified or amidated CO₂H; X = (un)substituted divalent hydrocarbon residue; R2 = H or (un)substituted hydrocarbon residue; R3 = alkyl which is substituted with a group bonded through O or S(O)_n (n = 0, 1, or 2); with proviso that when NHXCO is a Leu residue, R3 ≠ 3-hydroxy-3-methylbutyl nor 4-hydroxy-3-methylbutyl] and salts. I are useful as prophylactic and therapeutic agents for bone diseases (especially osteoporosis), and as inhibitors of thiol protease. For example, peptide coupling of H-Phe-OCH₂Ph.p-MeC₆H₄SO₃H with (2S,3S)-trans-Et hydrogen epoxysuccinate (77%), followed by hydrogenolytic deprotection (96%), amidation with MeO(CH₂)₃NH₂ (65%), and hydrolysis with aqueous NaOH in MeOH (85%), gave title compound II. In a test against human recombinant cathepsin L in vitro, II

had an IC50 of 3 ng/mL. I also suppressed bone resorption (142-176%) in mice.

ED Entered STN: 30 Mar 1996

L63 ANSWER 8 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:998130 HCAPLUS

DOCUMENT NUMBER: 124:176939

TITLE: Preparation of (aziridinylcarbonyl)amino acid amides as thiol protease inhibitors.

INVENTOR(S): Tsubotani, Shigetoshi; Takizawa, Masayuki; Shirasaki, Mikio; Mizoguchi, Junji; Shimizu, Yoshiaki

PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan

SOURCE: PCT Int. Appl., 143 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

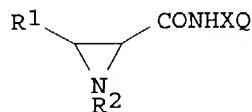
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9528416	A1	19951026	WO 1995-JP718	19950412
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TT, UA, US, UZ, VN				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2187451	AA	19951026	CA 1995-2187451	19950412
AU 9522235	A1	19951110	AU 1995-22235	19950412
EP 753003	A1	19970115	EP 1995-915310	19950412
EP 753003	B1	19990616		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AT 181333	E	19990715	AT 1995-915310	19950412
JP 08183767	A2	19960716	JP 1995-87885	19950413
US 5668128	A	19970916	US 1995-513896	19950905
PRIORITY APPLN. INFO.:			JP 1994-74621	19940413
			JP 1994-269175	19941101
			WO 1995-JP718	19950412

OTHER SOURCE(S): MARPAT 124:176939
GI



I

AB Title compds. [I; R1, Q = (esterified or amidated) carboxy; R2 = H, acyl, (substituted) hydrocarbyl; X = (substituted) divalent hydrocarbyl], were prepared Thus, N-[N-[(2S,3S)-3-carboxyaziridine-2-carbonyl]-L-phenylalanyl]-1,4-diaminobutane (II) (solution phase preparation given) inhibited cathepsin L with IC50 = 3 ng/mL, and at 10 µg/mL gave 99% inhibition of parathyroid hormone-enhanced mouse bone resorption. A capsule formulation containing II is given.

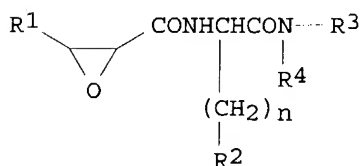
ED Entered STN: 22 Dec 1995

L63 ANSWER 9 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:886024 HCAPLUS
 DOCUMENT NUMBER: 123:286713
 TITLE: Preparation of epoxysuccinic acid-derivative
 inhibitors of **thiol** proteases for treatment
 of osteoporosis
 INVENTOR(S): Tsubotani, Shigetoshi; **Takizawa, Masayuki**;
 Shirasaki, Mikio; Fujisawa, Yukio
 PATENT ASSIGNEE(S): **Takeda Chemical Industries, Ltd., Japan**
 SOURCE: Eur. Pat. Appl., 95 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 655447	A1	19950531	EP 1994-307984	19941028
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
US 5556853	A	19960917	US 1994-330833	19941027
CA 2134627	AA	19950430	CA 1994-2134627	19941028
FI 9405092	A	19950430	FI 1994-5092	19941028
NO 9404121	A	19950502	NO 1994-4121	19941028
AU 9477552	A1	19950518	AU 1994-77552	19941028
CN 1112555	A	19951129	CN 1994-118687	19941028
JP 08104683	A2	19960423	JP 1994-265686	19941028
HU 72319	A2	19960429	HU 1994-3116	19941028
PRIORITY APPLN. INFO.:			JP 1993-272806	A 19931029
			JP 1993-272835	A 19931029
			JP 1994-186165	A 19940808

OTHER SOURCE(S): MARPAT 123:286713
 GI



AB The title compds. [I; R1 = (un)substituted carboxyl group; R2 = (un)substituted cyclic group; R3 = H, (un)substituted hydrocarbon residue; R4 = (un)substituted hydrocarbon residue with optionally protected amino group, alkenyl; n = 0-6; R3R4N = heterocyclic residue], which are inhibitors of **thiol** proteases such as cathepsin L or B, useful as prophylactic and/or therapeutic agents for bone diseases such as osteoporosis, are prepared and I-containing formulations presented. Thus, N-Z-N'-[N-(2S,3S)-trans-carboxyoxirane-2-carbonyl]-o-fluoro-L-phenylalanyl]-1,4-diaminobutane (sic) was prepared and demonstrated a IC50 of 1 ng/mL against cathepsin L and 14 ng/mL against cathepsin B.

ED Entered STN: 31 Oct 1995

L63 ANSWER 10 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1991:102698 HCAPLUS
 DOCUMENT NUMBER: 114:102698

TITLE: Preparation of saccharoascorbic acid derivatives as antioxidant food additives and synthetic intermediates.

INVENTOR(S): Matsumura, Koichi; Shimizu, Yoshiaki; Yamashita, Toshiro; Sugihara, Yoshihiro; Iida, Kouichi

PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan

SOURCE: Eur. Pat. Appl., 67 pp.
CODEN: EPXXDW

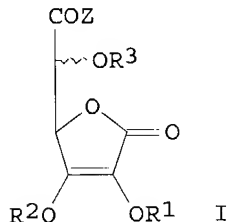
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 381472	A1	19900808	EP 1990-301004	19900131
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL				
CA 2009006	AA	19900731	CA 1990-2009006	19900131
CN 1044655	A	19900815	CN 1990-100429	19900131
JP 02282379	A2	19901119	JP 1990-23400	19900131
JP 02282380	A2	19901119	JP 1990-23401	19900131
JP 02288872	A2	19901128	JP 1990-23402	19900131
US 5043459	A	19910827	US 1990-473154	19900131
PRIORITY APPLN. INFO.:			JP 1989-23481	A 19890131
			JP 1989-23482	A 19890131
			JP 1989-23483	A 19890131
OTHER SOURCE(S):		MARPAT 114:102698		
GI				



AB The title compds. [I; Z = NR₄R₅, SR₆, OR₇; R₄, R₅, R₆, R₇ = C₁-24 hydrocarbyl; or R₄R₅ = (CH₂)_n; n = 4-7; R₁, R₂, R₃ = H, C₁-18 acyl, C₁-24 hydrocarbyl; provided that when Z = OR₇, R₁ ≠ R₂ and R₃ = H], also useful as intermediates for dichiral compds., e.g. liquid crystals, and antithrombotics, are prepared, e.g. by reaction of I (Z = OH; R₂, R₂ = protective group R₃ = same as above) with HNR₄R₅ or R₆SH. Thus, treatment of 5-O-acetyl-2,3-di-O-benzyl-β-glucosaccharoascorbic acid (II) with PC15 in Cl₂CH₂ and amidation of the resulting acid chloride with n-C₁₀H₂₁NH₂ in Cl₂CH₂ gave 75.8% n-decylamide of II which was deacetylated with 2N aqueous H₂SO₄-MeCN in 63.3% yield and then hydrogenolyzed over 5% Pd/C in EtOAc to give 74.8% n-decylamide of D-glucosaccharoascorbic acid (III). III had the same level of reducing activity as that of D-glucosaccharoascorbic acid. A total of 71 I were prepared

ED Entered STN: 23 Mar 1991

L63 ANSWER 11 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1987:67102 HCAPLUS

DOCUMENT NUMBER: 106:67102

TITLE: Lactams and thiolactams as antiinflammatory

agents
 INVENTOR(S): Imai, Naohiro; Fuse, Yoshihide; Katsumi, Ikuo;
 Yamashita, Katsuji; Hidaka, Takayasu; Hosoe, Kazunori;
 Ariki, Yutaka; **Yamashita, Toshiaki**;
 Watanabe, Kiyoshi
 PATENT ASSIGNEE(S): Kanegafuchi Chemical Industry Co., Ltd., Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 14 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 61218571	A2	19860929	JP 1985-58971	19850323
JP 06023194	B4	19940330		

PRIORITY APPLN. INFO.: JP 1985-58971 19850323

GI For diagram(s), see printed CA Issue.

AB (Thio)lactams I (R1 = H, C1-8 alkyl, PhCH2, acyl; R2 = H, C1-6 alkyl; R3, R4 = H, R3R4 = bond, R5 = H, C1-3 alkyl, acyl; X = O, S; n = 2-5), effective antiinflammatory agents at 50 mg/kg p.o. in rats, are prepared Thus, a solution of 8.19 g aldehyde II and 3.56 g **pyrrolidone** III in THF was added to a suspension of 3.36 g 60 weight% oily NaH in THF under N and cooling, stirred at room temperature, and hydrolyzed to give 47% I (R1 = R2 = R5 = H, R3R4 = bond, X = O, n = 2).

ED Entered STN: 07 Mar 1987

L63 ANSWER 12 OF 20 MEDLINE on STN

ACCESSION NUMBER: 2000226992 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10765925

TITLE: Production of tissue inhibitor of metalloproteinases 3 is selectively enhanced by calcium pentosan polysulfate in human rheumatoid synovial fibroblasts.

AUTHOR: **Takizawa M**; Ohuchi E; Yamanaka H; Nakamura H; Ikeda E; Ghosh P; Okada Y

CORPORATE SOURCE: Keio University, and Grelan Pharmaceutical Co., Tokyo, Japan.

SOURCE: Arthritis and rheumatism, (2000 Apr) 43 (4) 812-20.
 Journal code: 0370605. ISSN: 0004-3591.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 200005

ENTRY DATE: Entered STN: 20000525

Last Updated on STN: 20000525

Entered Medline: 20000518

AB OBJECTIVE: To determine the effects of calcium pentosan polysulfate (CaPPS) on the production of matrix metalloproteinases (**MMPs**) and their endogenous inhibitors, tissue inhibitors of metalloproteinases (TIMP), in cultures of rheumatoid synovial fibroblasts. METHODS: The production of **MMP**-1, -2, -3, -7, -8, -9, and -13 and of TIMP-1, -2, -3, and -4 in cultured rheumatoid synovial fibroblasts treated with 0.1, 1, and 10 microg/ml CaPPS in the presence and absence of 100 units/ml interleukin-1alpha (IL-1alpha) was examined by a sandwich enzyme immunoassay system and/or immunoblotting. The messenger RNA (mRNA) expression of TIMP-3 and membrane type 1 **MMP** was determined by Northern blotting, and the cells expressing TIMP-3 gene in rheumatoid synovium were identified by in situ hybridization. The synthesis and

secretion of TIMP-3 protein were monitored by pulse-chase experiments. TIMP-3 was immunolocalized in untreated or CaPPS-treated rheumatoid synovial fibroblasts and synovium using an avidin-biotin-peroxidase complex method. RESULTS: Treatment of cultured rheumatoid synovial fibroblasts with CaPPS resulted in a dose-dependent increase in the production of TIMP-3 in both cell lysates and media from the treated cells. However, CaPPS did not affect the levels of the other MMPs or TIMPs examined. The production of TIMP-3 was further enhanced in the cells treated with both IL-1alpha and CaPPS. Immunohistochemistry confirmed the enhanced production of TIMP-3 by cells exposed to CaPPS. The mRNA level of TIMP-3 increased 3.4-fold by treating rheumatoid synovial fibroblasts with IL-1alpha, but CaPPS itself did not alter the expression levels in the IL-1alpha-treated or -untreated cells. Pulse-chase studies demonstrated that translation for TIMP-3 protein was enhanced by CaPPS treatment. In situ hybridization and immunohistochemistry indicated that TIMP-3 was expressed mainly in the hyperplastic lining cells of rheumatoid synovium, and that the production of this protein by these immunoreactive lining cells was significantly increased by treatment with CaPPS. CONCLUSION: The present study is the first to demonstrate that the new antiarthritic drug, CaPPS, selectively enhanced TIMP-3 production at the posttranscription level in cultured rheumatoid synovial fibroblasts and in the lining cells of rheumatoid synovium. By this mechanism, CaPPS may be able to modulate joint tissue destruction in rheumatoid arthritis.

ED Entered STN: 20000525
Last Updated on STN: 20000525
Entered Medline: 20000518

L63 ANSWER 13 OF 20 MEDLINE on STN
ACCESSION NUMBER: 88299969 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2457066
TITLE: Oligo-2',5'-adenylate synthetase activity in K562 cell lines persistently infected with measles or mumps virus.
AUTHOR: Fujii N; Oguma K; Kimura K; Yamashita T; Ishida S; Fujinaga K; Yashiki T
CORPORATE SOURCE: Department of Microbiology, Sapporo, Medical College, Japan.
SOURCE: Journal of general virology, (1988 Aug) 69 (Pt 8) 2085-91. Journal code: 0077340. ISSN: 0022-1317.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198809
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19880916

AB Fluctuation of oligo-2',5'-adenylate synthetase (2-5AS) activity was examined in K562 cells infected with vaccine strains of measles virus (strains AIK-C and CAM-70) and mumps virus (strains Torii and Miyahara). Persistent infection was easily established in the mumps virus-infected cells without significant cytolysis or cell killing. In contrast, most of the cells infected with measles virus were killed by extensive cytolysis within 3 to 4 days. The small number of cells that did survive became persistently infected. That these persistently infected cells carried a virus antigen was confirmed by fluorescein isothiocyanate-labelled anti-measles virus rabbit antiserum and anti-mumps virus rabbit antiserum. The cells produced infectious progeny virus as well as interferon (IFN). Little induction of 2-5AS activity by IFN was demonstrated during the early stages of infection by these viruses.

Similar results were observed in some of the persistently infected cells but not, however, K-CMP cells (K562 cells persistently infected with CAM-70) or K-MMP cells (K562 cells persistently infected with Miyahara). Failure to induce 2-5AS activity was unchanged in cells cultured for more than 6 months. The decrease of 2-5AS activity observed in K-MTP cells (K562 cells persistently infected with Torii) was the result of suppression of transcription of 2-5AS mRNA. On the other hand, a normal level of mRNA was found in K-AKP cells (K562 cells persistently infected with AIK-C). Therefore, it is suggested that the decrease of 2-5AS activity in K-AKP cells may be due to a failure to translate 2-5AS mRNA.

ED Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19880916

L63 ANSWER 14 OF 20 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2002:475379 BIOSIS
DOCUMENT NUMBER: PREV200200475379
TITLE: Thiol compounds, their production and use.
AUTHOR(S): Yamashita, Toshiro [Inventor, Reprint author];
Nara, Hiroshi [Inventor]; Takizawa,
Masayuki [Inventor]; Yoshimura, Koji
[Inventor]
CORPORATE SOURCE: Tsukuba, Japan
ASSIGNEE: Takeda Chemical Industries, Ltd., Osaka,
Japan
PATENT INFORMATION: US 6420415 July 16, 2002
SOURCE: Official Gazette of the United States Patent and Trademark
Office Patents, (July 16, 2002) Vol. 1260, No. 3.
<http://www.uspto.gov/web/menu/patdata.html>. e-file.
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 11 Sep 2002
Last Updated on STN: 11 Sep 2002

AB Compounds represented by general formula (1) or salts thereof which have a matrix **metalloprotease** inhibitory activity and are useful as drugs, wherein the rings A and B represent each an optionally substituted homocycle or heterocycle, etc.; R1 s are the same or different and each represents hydrogen, optionally substituted hydrocarbyl, acyl, etc.; X1 represents a bond, optionally substituted divalent aliphatic hydrocarbyl, etc.; X2 represents a bond, optionally substituted divalent aliphatic hydrocarbyl, --O--, etc.; Ys are the same or different represents hydrogen, optionally substituted hydrocarbyl, oxo, etc.; m is 0 or 1; n is an integer of 1 to 3; q1 is an integer of 1 to 2n+4; and q2 is an integer of 0 to 2n+3, provided that q1 +q2 is 2n+4. ##STR1##

ED Entered STN: 11 Sep 2002
Last Updated on STN: 11 Sep 2002

L63 ANSWER 15 OF 20 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001351101 EMBASE
TITLE: Expression of membrane-type matrix metalloproteinases in synovial tissue from patients with rheumatoid arthritis or osteoarthritis.
AUTHOR: Mitsui H.; Tsuchiya N.; Okinaga S.; Matsuta K.;
Yoshimura K.; Nishimura A.
CORPORATE SOURCE: A. Nishimura, Discovery Research Laboratories II,
Pharmaceutical Discovery Res. Div., Takeda

SOURCE: Chemical Industries Ltd., 10 Wadai, Tsukuba 300-4247, Japan
Modern Rheumatology, (2001) 11/1 (34-39).
Refs: 30
ISSN: 1439-7595 CODEN: MROHA4

COUNTRY: Japan

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry
031 Arthritis and Rheumatism
033 Orthopedic Surgery
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB We investigated the expression of membrane-type metalloproteinase (MT-MMP) and matrix metalloproteinase (MMP) mRNAs in synovial tissue from patients with rheumatoid arthritis (RA, n = 5) or osteoarthritis (OA, n = 5) by Northern blot analysis. Northern analysis demonstrated strong expression of MT1-MMP, MT3-MMP, MMP-1, and MMP-3 and weak expression of MT2-MMP and MMP-8 in synovial tissue from patients with RA or OA. MT4-MMP was not detected. No significant difference was shown in the expression of MT-MMP mRNAs between RA and OA. Synovial tissue of RA or OA patients expressed MT-MMPs as well as MMPs. These results indicate that, in addition to MMPs, MT1-MMP, MT3-MMP, and probably MT2-MMP may play a role in the degradation of bone and cartilage matrix in RA and OA. Such information may provide a clue to the development of a novel therapeutic approach targeted on the prevention of joint destruction.

L63 ANSWER 16 OF 20 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

ACCESSION NUMBER: 2003-372019 [35] WPIX

DOC. NO. NON-CPI: N2003-296671

DOC. NO. CPI: C2003-098842

TITLE: Screening promoters or inhibitors of proteoglycan decomposition as preventives for bone and joint diseases with use of cells expressing matrix metalloproteinase (MMP)-19 and membrane-type (MT)3-MMP, particularly for rheumatoid arthritis.

DERWENT CLASS: B04 D16 S03

INVENTOR(S): HIKICHI, Y; YOSHIMURA, K

PATENT ASSIGNEE(S): (TAKE) TAKEDA CHEM IND LTD

COUNTRY COUNT: 100

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003029819	A1	20030410	(200335)*	JA	96
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
JP 2003189898	A	20030708	(200354)		38
AU 2002338108	A1	20030414	(200461)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
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WO 2003029819	A1	WO 2002-JP9949	20020926
JP 2003189898	A	JP 2002-280158	20020926
AU 2002338108	A1	AU 2002-338108	20020926

FILING DETAILS:

PATENT NO	KIND	PATENT NO
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AU 2002338108	A1 Based on	WO 2003029819

PRIORITY APPLN. INFO: JP 2001-303314 20010928

AN 2003-372019 [35] WPIX

AB WO2003029819 A UPAB: 20030603

NOVELTY - Screening compounds or their salts promoting or inhibiting proteoglycan decomposition is by using a combination of a protein based on the sequence of (I) of 508 amino acids, and another protein with an amino acid sequence identical or substantially similar to that of (II) of 457 amino acids, its partial peptide, is new. Both sequences given in the specification.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a similar method using DNA encoding the proteins with amino acids sequences of (I) and (II), or cells co-expressing the proteins or their partial peptide, optionally in the presence of animal-originated cartilage tissues or cells for co-culturing with a test compound, and measuring the proteoglycan decomposition activity with a control run for comparison;

(2) kits for screening compounds or their salts promoting or inhibiting proteoglycan decomposition containing the proteins or their partial peptides, or DNA encoding them, or cells expressing them;

(3) promoters or inhibitors of proteoglycan decomposition;

(4) drugs containing the thus screened promoters or inhibitors;

(5) preventives or remedies containing these screened compounds or their salts that inhibit or promote proteoglycan decomposition, or activity of the protein with an amino acid sequence of (I), its variant, their partial peptide or salts;

(6) preventing or treating bone and joint diseases by administering an effective dose of the compounds or their salts inhibiting or promoting activity of the protein with an amino acid sequence of (I) or its derivative; and

(7) the use of inhibitors or promoters of activity of the protein with an amino acid sequence of (I) or its derivative for producing preventives or remedies for bone and joint diseases.

ACTIVITY - Osteopathic.

No biological data is given.

MECHANISM OF ACTION - None given.

USE - The method is promoters or inhibitors of proteoglycan decomposition as preventives or remedies for bone and joint diseases, e.g. rheumatoid arthritis, osteoporosis and arthritis deformans (all claimed).

ADVANTAGE - With this method, the compounds regulating the decomposition activity of proteoglycan can be efficiently selected.

Dwg.0/0

ED 20030603

L63 ANSWER 17 OF 20 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

ACCESSION NUMBER: 2003-313193 [30] WPIX

DOC. NO. NON-CPI: N2003-249329

DOC. NO. CPI: C2003-082194

TITLE: Substances regulating the activity of proteins having increased expression in bone and joint disease for treatment and prevention of these diseases.

DERWENT CLASS: B04 D16 S03

INVENTOR(S): HIKICHI, Y; INAZUKA, M; YOSHIMURA, K
 PATENT ASSIGNEE(S): (TAKE) TAKEDA CHEM IND LTD
 COUNTRY COUNT: 101
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003022300	A1	20030320	(200330)*	JA	154
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
JP 2003183177	A	20030703	(200352)		66
EP 1426056	A1	20040609	(200438)	EN	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR					
AU 2002335369	A1	20030324	(200461)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003022300	A1	WO 2002-JP9140	20020909
JP 2003183177	A	JP 2002-262564	20020909
EP 1426056	A1	EP 2002-798045	20020909
		WO 2002-JP9140	20020909
AU 2002335369	A1	AU 2002-335369	20020909

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1426056	A1 Based on	WO 2003022300
AU 2002335369	A1 Based on	WO 2003022300

PRIORITY APPLN. INFO: JP 2001-303390 20010928; JP
 2001-273914 20010910; JP
 2001-281472 20010917; JP
 2001-300289 20010928; JP
 2001-300347 20010928; JP
 2001-300417 20010928

AN 2003-313193 [30] WPIX

AB WO2003022300 A UPAB: 20030513

NOVELTY - Agents for the treating and preventing bone and joint diseases which regulate the activity or expression of human proteins (I) showing increased expression in diseased bone and joint tissue e.g. DIO2 (type 2 iodothyronine deiodinase); ANKH (pyrophosphate transporter); SHOX2 (short stature homeobox 2); TASK4 (potassium ion channel protein); EphA3 (Eph receptor A3); and/or **MMP16** (matrix metalloproteinase 16), are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for
 (1) agents for prevention and treatment of bone and joint diseases, containing DNA complementary to all or part of DNA encoding proteins (I), or containing antibodies to proteins (I);
 (2) diagnostic reagents for bone and joint diseases, containing DNA complementary to all or part of DNA encoding proteins (I), or containing antibodies to proteins (I);

(3) screening agents for the treatment and prevention of bone and joint diseases, in which the effect of the test substance on the activity or expression of proteins (I) is determined;

(4) kits for the screening method;

(5) agents for the treatment and prevention of bone and joint diseases, identified by the method;

(6) treatment and prevention of bone and joint diseases, using the agents of (5).

ACTIVITY - Antiarthritic; Antirheumatic; Osteopathic; Antiinflammatory.

MECHANISM OF ACTION - Iodothyronine deiodinase inhibitor; Pyrophosphate transport inhibitor; Short stature homeobox 2 inhibitor; Potassium ion transport inhibitor; Eph receptor antagonist; Matrix metalloproteinase 16 inhibitor.

USE - Prevention, treatment and diagnosis of diseases involving abnormal formation or development of bone and cartilage (such as arthritis deformans), chronic rheumatoid arthritis, synovial inflammation, or localized arthritis (such as 'tennis elbow').

Dwg.0/4

ED 20030513

L63 ANSWER 18 OF 20 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2002-227106 [28] WPIX
 DOC. NO. NON-CPI: N2002-174317
 DOC. NO. CPI: C2002-069140
 TITLE: Transgenic mammal containing foreign **MMP-19** gene for use as a model for bone and cartilage diseases.
 DERWENT CLASS: B04 D16 P14 S03
 INVENTOR(S): HOSONO, K; NISHIDA, M; NISHIMURA, A; YOSHIMURA, K
 PATENT ASSIGNEE(S): (TAKE) **TAKEDA CHEM IND LTD**
 COUNTRY COUNT: 95
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002011530	A1	20020214	(200228)*	JA	47
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001077716	A	20020218	(200244)		
JP 2002360117	A	20021217	(200312)		18

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002011530	A1	WO 2001-JP6826	20010808
AU 2001077716	A	AU 2001-77716	20010808
JP 2002360117	A	JP 2001-240948	20010808

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001077716	A Based on	WO 2002011530

PRIORITY APPLN. INFO: JP 2000-241748 20000809

AN 2002-227106 [28] WPIX
 AB WO 200211530 A UPAB: 20020502
 NOVELTY - Non-human transgenic mammal containing recombinant DNA encoding a foreign **MMP-19** gene or its modified form is new.
 DETAILED DESCRIPTION - Non-human transgenic mammal transformed with recombinant DNA encoding a foreign **MMP-19** gene or its modified form is new, . INDEPENDENT CLAIMS are also included for:
 (1) cover expression vectors for **MMP-19** gene in non-human mammals;
 (2) cells transformed by the vectors;
 (3) a method for screening compounds for use in the prevention and treatment of extracellular matrix disorders, using the transgenic mammals;
 (4) compounds identified by the screening method;
 (5) a method for treatment of extracellular matrix disorders using the identified compounds;
 (6) fertilized ova transformed by the foreign **MMP-19** gene;
 and
 (7) the production of transgenic mammals by implantation of the ova and bringing to term.
 ACTIVITY - Osteopathic; Antiarthritic; Antirheumatic; Ophthalmological; Cytostatic.
 MECHANISM OF ACTION - None given.
 USE - Identification of agents for the treatment and prevention of extracellular matrix disorders including chondrogenic failure, osteogenetic failure, osteoporosis, arthritis deformans, rheumatoid arthritis, synovitis, metabolic arthritis, eye disease, malignant tumors, and associated complications. The transgenic mammals are a model for joint and bone diseases including deformation and shortening of limbs, cranial deformation, defective bite, tooth elongation, and defects of lumbar and tail vertebrae.
 Dwg.0/3
 ED 20020502

L63 ANSWER 19 OF 20 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2000-271056 [23] WPIX
 DOC. NO. CPI: C2000-082646
 TITLE: Novel protein belong to A disintegrin and **metalloprotease** family, with protease activity and extracellular matrix digesting enzyme activity, for gene diagnosis and developing drugs for treating e.g. sciatica and glomerulitis.
 DERWENT CLASS: B04 D16
 INVENTOR(S): HIKICHI, Y; NISHIMURA, A; **YOSHIMURA, K**
 PATENT ASSIGNEE(S): (TAKE) **TAKEDA CHEM IND LTD**; (HIKI-I) HIKICHI Y;
 (NISH-I) NISHIMURA A; (YOSH-I) YOSHIMURA K
 COUNTRY COUNT: 88
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000014227	A1	20000316	(200023)*	JA	108
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL					
OA PT SD SE SL SZ UG ZW					
W: AE AL AM AU AZ BA BB BG BR BY CA CN CR CU CZ DM EE GD GE HR HU ID					
IL IN IS JP KG KR KZ LC LK LR LT LV MD MG MK MN MX NO NZ PL RO RU					
SG SI SK SL TJ TM TR TT UA US UZ VN YU ZA					
AU 9954479	A	20000327	(200032)		
JP 2000139480	A	20000523	(200033)		48
EP 1111047	A2	20010627	(200137)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT					

RO SE SI

JP 2000568971 X 20011120 (200203)
 US 6680189 B1 20040120 (200407)
 US 2004132157 A1 20040708 (200445)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000014227	A1	WO 1999-JP4766	19990902
AU 9954479	A	AU 1999-54479	19990902
JP 2000139480	A	JP 1999-248436	19990902
EP 1111047	A2	EP 1999-940629	19990902
		WO 1999-JP4766	19990902
JP 2000568971	X	WO 1999-JP4766	19990902
		JP 2000-568971	19990902
US 6680189	B1	WO 1999-JP4766	19990902
		US 2001-786256	20010510
US 2004132157	A1 Div ex	WO 1999-JP4766	19990902
	Div ex	US 2001-786256	20010510
		US 2003-726148	20031202

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9954479	A Based on	WO 2000014227
EP 1111047	A2 Based on	WO 2000014227
JP 2000568971	X Based on	WO 2000014227
US 6680189	B1 Based on	WO 2000014227
US 2004132157	A1 Div ex	US 6680189

PRIORITY APPLN. INFO: JP 1998-250115 19980903

AN 2000-271056 [23] WPIX

AB WO 200014227 A UPAB: 20000516

NOVELTY - Protein (I) comprising a sequence of 96 amino acids (aa), given in the specification, or its salt, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(i) a peptide fragment of (I) or its salt which comprising a sequence of 10 aa (II), given in the specification;

(ii) a DNA encoding (I);

(iii) a DNA (III) comprising a sequence of 288 base pairs (bp), given in the specification, encoding a fragment of (I);

(iv) a recombinant vector containing a DNA encoding (I);

(v) a transformant obtained with the recombinant vector of (iv);

(vi) producing (I) or its salt by culturing the transformant of (v);

(vii) an antibody with specificity to (I), its peptide fragments or salts;

(viii) a diagnostic reagent comprising the DNA encoding (I) or antibody of (vii);

(ix) an agent comprising (I), its fragments or salts;

(x) a drug comprising (I), its fragments or salts, which can be used to prevent or treat intervertebral hernia, sciatica, glomerulitis, diabetic nephropathy, hepatic fibrosis, pulmonary fibrosis or osteopetrosis;

(xi) screening for compounds or salts that can promote or inhibit the protease activity by using the protein or its salt;

(xii) a kit for screening for compounds or salts capable of promoting or inhibiting the protease activity containing the protein or its salt;

- (xiii) protease promoters or inhibitors identified by the screen of (xi);
- (xiv) drugs containing the protease promoters or inhibitors of (xiii);
- (xv) an extracellular matrix digesting agent comprising a protein with 201 aa sequence ((IV); given in the specification), where the extracellular matrix is a proteoglycan, and can be used to prevent or treat intervertebral hernia, sciatica, glomerulitis, diabetic nephropathy, hepatic fibrosis, pulmonary fibrosis or osteopetrosis;
- (xvi) a drug composition containing the agent of (xv);
- (xvii) screening for compounds or salts capable of promoting or inhibiting the extracellular matrix digesting enzyme activity using (IV);
- (xviii) kits comprising (I) or its salt, for screening for compounds or salts that can promote or inhibit the extracellular matrix digesting enzyme activity;
- (xix) promoters or inhibitors of the extracellular matrix digesting enzyme activity obtained using the kits of (xviii);
- (xx) drugs containing the promoters or inhibitors of the extracellular matrix digesting enzyme activity;
- (xxi) a diagnostic reagent comprising (I) or its salt;
- (xxii) detecting a proteoglycan digesting enzyme gene by culturing a recombinant host containing the gene, and animal-derived cartilage or cartilage matrix-producing cells, and determining the amount of glycosaminoglycan sulfate in the culture supernatant solution;
- (xxiii) screening for inhibitors or promoters of the proteoglycan digesting enzyme comprising:
- (a) introducing a protein with proteoglycan digesting enzyme activity, preferably comprising (I) and/or (IV), to a transformant, or particularly an animal cell;
- (b) obtaining animal-derived cartilage or cartilage matrix-producing cells and mix-culturing with a sample; and
- (c) determining the glycosaminoglycan sulfate in the culture supernatant solution; and
- (xxiv) a non-human animal containing (and expressing) a DNA encoding (I), or its variants.

Glu Cys Thr Asn Ile Cys Cys Asp Ala Lys (II)

USE - The protein, peptide fragment and antibody are useful for gene diagnosis and in the development of drugs to prevent or treat intervertebral hernia, sciatica, glomerulitis, diabetic nephropathy, hepatic fibrosis, pulmonary fibrosis or osteopetrosis (claimed).

ADVANTAGE - The protein belongs to the ADAM family.

Dwg.0/5

ED 20000516

L63 ANSWER 20 OF 20 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
 ACCESSION NUMBER: 1997-535841 [49] WPIX
 DOC. NO. CPI: C1997-171397
 TITLE: New matrix **metalloprotease** from human or rat -
 useful for treatment, prevention and diagnosis of e.g.
 diabetic nephropathy, glomerulonephritis, fibrosis, liver
 cirrhosis etc..
 DERWENT CLASS: B04 D16
 INVENTOR(S): HIKICHI, Y; NISHIMURA, A; YOSHIMURA, K;
 ATSUSHI, N; KOJI, Y; YUICHI, H
 PATENT ASSIGNEE(S): (TAKE) **TAKEDA CHEM IND LTD**
 COUNTRY COUNT: 76
 PATENT INFORMATION:

PATENT NO	KIND DATE	WEEK	LA	PG

WO 9740157 A1 19971030 (199749)* EN 117
 RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT
 SD SE SZ UG
 W: AL AM AU AZ BA BB BG BR BY CA CN CU CZ EE GE HU IL IS KG KR KZ LC
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 US UZ VN YU
 AU 9724064 A 19971112 (199811)
 JP 10080283 A 19980331 (199823) 42
 EP 897426 A1 19990224 (199912) EN
 R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
 US 6566116 B1 20030520 (200336)
 US 2003099631 A1 20030529 (200337)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9740157	A1	WO 1997-JP1433	19970424
AU 9724064	A	AU 1997-24064	19970424
JP 10080283	A	JP 1997-106511	19970424
EP 897426	A1	EP 1997-919679	19970424
		WO 1997-JP1433	19970424
US 6566116	B1	WO 1997-JP1433	19970424
		US 1999-171545	19990726
US 2003099631	A1 Div ex	WO 1997-JP1433	19970424
	Div ex	US 1999-171545	19990726
		US 2002-251482	20020919

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9724064	A Based on	WO 9740157
EP 897426	A1 Based on	WO 9740157
US 6566116	B1 Based on	WO 9740157

PRIORITY APPLN. INFO: JP 1996-104902 19960425

AN 1997-535841 [49] WPIX

AB WO 9740157 A UPAB: 19971211

A protein (A), with the 508 amino acid (aa) sequence given in the specification, its salts, and its equivalents, are new. Also new are: (1) an active fragment (Aa) of (A); (2) a DNA (I) encoding (A) (sequences of 1524 bp (human) and 1551 bp (rat) given in the specification); (3) a recombinant vector containing (I); (4) a cell transformed with the vector of (3); (5) an antibody (Ab) against (A) and (Aa); (6) a method (and kit) for screening to identify compounds (B) that activate or inhibit (A) and (Aa); and (7) (B) identified by the method of (6).

USE - (A), is a matrix **metalloprotease**. (A), (Aa) and (B) that activate (A) are useful for treating or preventing conditions in which endogenous (A) activity is suppressed, specifically diabetic nephropathy, glomerulonephritis, pulmonary fibrosis, hepatolinal fibrosis, hepatocirrhosis, osteopetrosis and herniated discs. (A) and (Aa) are also used in the screening method of (6). (I) are used to produce recombinant (A) and (Aa), also for gene therapy of the specified conditions (all claimed). Fragments of (I) can be used to detect genetic abnormalities. Ab are used for quantitative immunoassay of (A) or (Aa), particularly for diagnosis, also for histological staining and for purification of (A). (B) which are inhibitors (including antisense nucleic acid) are useful for treating or preventing a wide range of conditions where (A) levels are elevated, e.g. wounds, rheumatoid arthritis,

osteoarthritis, cancer (including metastases), corneal or gastric ulcers, atherosclerosis, multiple sclerosis, cachexia, lymphoma, diabetes, asthma (and other allergies), acute pancreatitis, myocardial infarction, graft vs. host disease etc. Also, transgenic animals that overexpress (A) can be used to screen for (B), as a source of cells for studying the function of (A) and for the production of (A).

Dwg.0/6

ED 19971211

=>

=>

3/5

=> fil lreg

FILE 'LREGISTRY' ENTERED AT 11:02:47 ON 27 NOV 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE 'REGISTRY' ENTERED AT 11:02:50 ON 27 NOV 2004
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STRUCTURE FILE UPDATES: 25 NOV 2004 HIGHEST RN 788788-78-3
DICTIONARY FILE UPDATES: 25 NOV 2004 HIGHEST RN 788788-78-3

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

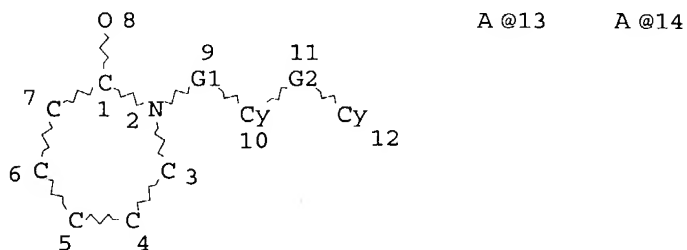
Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> d que 132

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L2 STR



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REP G2=(0-6) 14

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NSPEC IS RC AT 14

CONNECT IS E1 RC AT 8

DEFAULT MLEVEL IS ATOM

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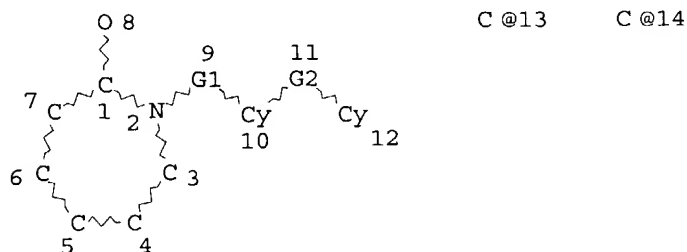
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NUMBER OF NODES IS 14

STEREO ATTRIBUTES: NONE

L3 3855 SEA FILE=REGISTRY SUB=L1 SSS FUL L2
 L16 STR



REP G1=(0-4) 13

REP G2=(0-4) 14

NODE ATTRIBUTES:

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NSPEC IS RC AT 14

CONNECT IS E1 RC AT 8

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

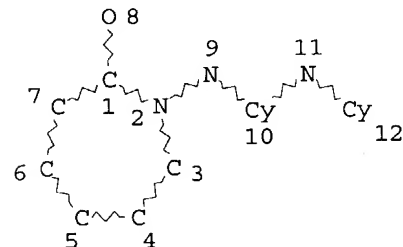
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RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 14

STEREO ATTRIBUTES: NONE

L18 STR



NODE ATTRIBUTES:

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NSPEC IS RC AT 11

CONNECT IS E1 RC AT 8

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

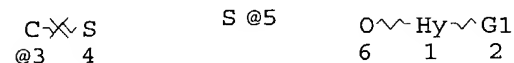
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NUMBER OF NODES IS 12

STEREO ATTRIBUTES: NONE

L21 3042 SEA FILE=REGISTRY SUB=L3 SSS FUL (L16 OR L18)

L30 STR



VAR G1=3/5

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 CONNECT IS E1 RC AT 6
 DEFAULT MLEVEL IS ATOM
 DEFAULT ECLEVEL IS LIMITED
 ECOUNT IS M6 C M1 N AT 1

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 6

STEREO ATTRIBUTES: NONE

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L33 ANALYZE L32 1- LC : 5 TERMS

=> d

L33 ANALYZE L32 1- LC : 5 TERMS

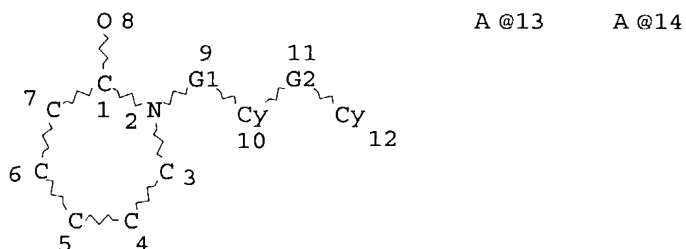
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L2 STR



REP G1=(0-6) 13

REP G2=(0-6) 14

NODE ATTRIBUTES:

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 CONNECT IS E1 RC AT 8
 DEFAULT MLEVEL IS ATOM
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

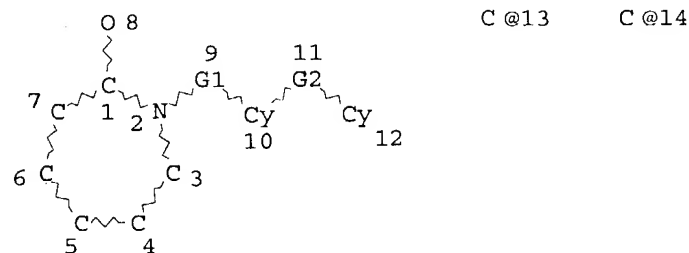
RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 14

STEREO ATTRIBUTES: NONE

L3 3855 SEA FILE=REGISTRY SUB=L1 SSS FUL L2

L16 STR



REP G1=(0-4) 13

REP G2=(0-4) 14

NODE ATTRIBUTES:

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CONNECT IS E1 RC AT 8

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

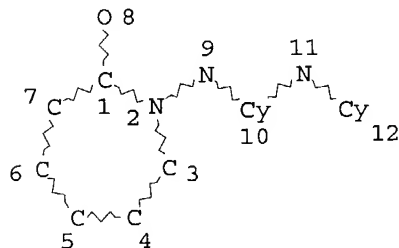
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RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 14

STEREO ATTRIBUTES: NONE

L18 STR



NODE ATTRIBUTES:

NSPEC IS RC AT 9

NSPEC IS RC AT 11

CONNECT IS E1 RC AT 8

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

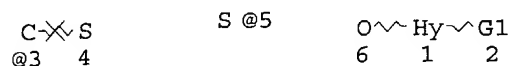
NUMBER OF NODES IS 12

STEREO ATTRIBUTES: NONE

L21 3042 SEA FILE=REGISTRY SUB=L3 SSS FUL (L16 OR L18)

L26 119 SEA FILE=REGISTRY ABB=ON PLU=ON L21 AND ?THIO?/CNS

L30 STR



VAR G1=3/5
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 NSPEC IS RC AT 4
 NSPEC IS RC AT 5
 CONNECT IS E1 RC AT 6
 DEFAULT MLEVEL IS ATOM
 DEFAULT ECLEVEL IS LIMITED
 ECOUNT IS M6 C M1 N AT 1

GRAPH ATTRIBUTES:
 RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 6

STEREO ATTRIBUTES: NONE
 L32 104 SEA FILE=REGISTRY SUB=L21 SSS FUL L30
 L42 22 SEA FILE=REGISTRY ABB=ON PLU=ON L26 NOT L32
 L43 2 SEA FILE=REGISTRY ABB=ON PLU=ON L42 AND ?SPIRO?/CNS

=> fil reg

FILE 'REGISTRY' ENTERED AT 11:35:21 ON 27 NOV 2004
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 provided by InfoChem.

STRUCTURE FILE UPDATES: 25 NOV 2004 HIGHEST RN 788788-78-3
 DICTIONARY FILE UPDATES: 25 NOV 2004 HIGHEST RN 788788-78-3

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when
 conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
 information enter HELP PROP at an arrow prompt in the file or refer
 to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> analyze l43
 ENTER ANSWER NUMBER OR RANGE (1-):1-
 ENTER DISPLAY CODE (CHEM) OR ?:lc
 L45 ANALYZE L43 1- LC : 5 TERMS

=> d
 L45 ANALYZE L43 1- LC : 5 TERMS

TERM #	# OCC	# DOC	% DOC	LC
1	2	2	100.00	CA
2	2	2	100.00	CAPLUS
3	1	1	50.00	TOXCENTER
4	1	1	50.00	USPATFULL

5 1 1 50.00 USPAT2
***** END OF L45***

=> file stnguide

FILE 'STNGUIDE' ENTERED AT 11:35:52 ON 27 NOV 2004
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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Nov 19, 2004 (20041119/UP).

=> => fil hcap

FILE 'HCAPLUS' ENTERED AT 11:38:52 ON 27 NOV 2004
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FILE COVERS 1907 - 27 Nov 2004 VOL 141 ISS 23
FILE LAST UPDATED: 26 Nov 2004 (20041126/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil uspatfull

FILE 'USPATFULL' ENTERED AT 11:38:56 ON 27 NOV 2004
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 25 Nov 2004 (20041125/PD)
FILE LAST UPDATED: 25 Nov 2004 (20041125/ED)
HIGHEST GRANTED PATENT NUMBER: US6823528
HIGHEST APPLICATION PUBLICATION NUMBER: US2004237163
CA INDEXING IS CURRENT THROUGH 25 Nov 2004 (20041125/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 25 Nov 2004 (20041125/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2004

>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<
>>> published document but also a list of any subsequent <<<
>>> publications. The publication number, patent kind code, and <<<

```

>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

>>> USPATFULL and USPAT2 can be accessed and searched together <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<

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This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil toxcenter

FILE 'TOXCENTER' ENTERED AT 11:38:59 ON 27 NOV 2004
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FILE COVERS 1907 TO 23 Nov 2004 (20041123/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

TOXCENTER has been enhanced with new files segments and search fields.
See HELP CONTENT for more information.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See <http://www.nlm.nih.gov/mesh/> and http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description of changes.

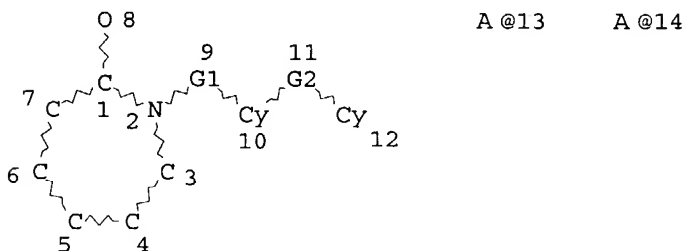
=> file stnguide

FILE 'STNGUIDE' ENTERED AT 11:39:03 ON 27 NOV 2004
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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Nov 19, 2004 (20041119/UP).

=> => d que 149

L1 (156603)SEA FILE=REGISTRY ABB=ON PLU=ON NC6/ESS
L2 STR

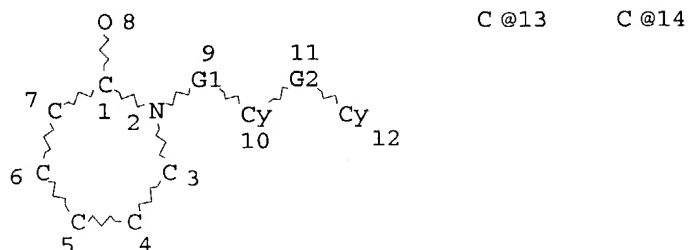


REP G1=(0-6) 13

REP G2=(0-6) 14
 NODE ATTRIBUTES:
 NSPEC IS RC AT 13
 NSPEC IS RC AT 14
 CONNECT IS E1 RC AT 8
 DEFAULT MLEVEL IS ATOM
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
 RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 14

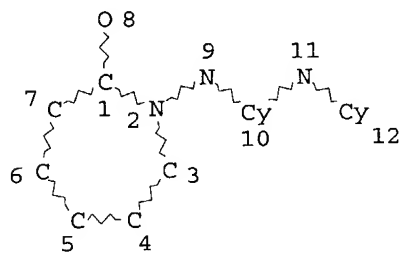
STEREO ATTRIBUTES: NONE
 L3 3855 SEA FILE=REGISTRY SUB=L1 SSS FUL L2
 L16 STR



REP G1=(0-4) 13
 REP G2=(0-4) 14
 NODE ATTRIBUTES:
 NSPEC IS RC AT 13
 NSPEC IS RC AT 14
 CONNECT IS E1 RC AT 8
 DEFAULT MLEVEL IS ATOM
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
 RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 14

STEREO ATTRIBUTES: NONE
 L18 STR



NODE ATTRIBUTES:
 NSPEC IS RC AT 9
 NSPEC IS RC AT 11
 CONNECT IS E1 RC AT 8
 DEFAULT MLEVEL IS ATOM
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 12

STEREO ATTRIBUTES: NONE

L21 3042 SEA FILE=REGISTRY SUB=L3 SSS FUL (L16 OR L18)
L26 119 SEA FILE=REGISTRY ABB=ON PLU=ON L21 AND ?THIO?/CNS
L30 STR

C~~X~~S S@5 O[~]Hy[~]G1
@3 4 6 1 2

VAR G1=3/5

NODE ATTRIBUTES:

NSPEC IS RC AT 3
NSPEC IS RC AT 4
NSPEC IS RC AT 5
CONNECT IS E1 RC AT 6
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED
ECOUNT IS M6 C M1 N AT 1

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 6

STEREO ATTRIBUTES: NONE

L32 104 SEA FILE=REGISTRY SUB=L21 SSS FUL L30
L34 13 SEA FILE=HCAPLUS ABB=ON PLU=ON L32
L42 22 SEA FILE=REGISTRY ABB=ON PLU=ON L26 NOT L32
L43 2 SEA FILE=REGISTRY ABB=ON PLU=ON L42 AND ?SPIRO?/CNS
L46 3 SEA FILE=HCAPLUS ABB=ON PLU=ON L43
L49 16 SEA FILE=HCAPLUS ABB=ON PLU=ON L34 OR L46

=> d que nos 150

L1 (156603)SEA FILE=REGISTRY ABB=ON PLU=ON NC6/ESS
L2 STR
L3 3855 SEA FILE=REGISTRY SUB=L1 SSS FUL L2
L16 STR
L18 STR
L21 3042 SEA FILE=REGISTRY SUB=L3 SSS FUL (L16 OR L18)
L26 119 SEA FILE=REGISTRY ABB=ON PLU=ON L21 AND ?THIO?/CNS
L30 STR
L32 104 SEA FILE=REGISTRY SUB=L21 SSS FUL L30
L36 9 SEA FILE=USPATFULL ABB=ON PLU=ON L32
L42 22 SEA FILE=REGISTRY ABB=ON PLU=ON L26 NOT L32
L43 2 SEA FILE=REGISTRY ABB=ON PLU=ON L42 AND ?SPIRO?/CNS
L47 4 SEA FILE=USPATFULL ABB=ON PLU=ON L43
L50 13 SEA FILE=USPATFULL ABB=ON PLU=ON L47 OR L36

=> d que nos 151

L1 (156603)SEA FILE=REGISTRY ABB=ON PLU=ON NC6/ESS
L2 STR
L3 3855 SEA FILE=REGISTRY SUB=L1 SSS FUL L2
L16 STR
L18 STR
L21 3042 SEA FILE=REGISTRY SUB=L3 SSS FUL (L16 OR L18)
L26 119 SEA FILE=REGISTRY ABB=ON PLU=ON L21 AND ?THIO?/CNS
L30 STR

L32 104 SEA FILE=REGISTRY SUB=L21 SSS FUL L30
 L37 1 SEA FILE=TOXCENTER ABB=ON PLU=ON L32
 L42 22 SEA FILE=REGISTRY ABB=ON PLU=ON L26 NOT L32
 L43 2 SEA FILE=REGISTRY ABB=ON PLU=ON L42 AND ?SPIRO?/CNS
 L48 2 SEA FILE=TOXCENTER ABB=ON PLU=ON L43
 L51 3 SEA FILE=TOXCENTER ABB=ON PLU=ON L37 OR L48

=> dup rem 149 150 151

FILE 'HCAPLUS' ENTERED AT 11:43:54 ON 27 NOV 2004
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 PROCESSING COMPLETED FOR L49
 PROCESSING COMPLETED FOR L50
 PROCESSING COMPLETED FOR L51
 L52 27 DUP REM L49 L50 L51 (5 DUPLICATES REMOVED)
 ANSWERS '1-16' FROM FILE HCAPLUS
 ANSWERS '17-27' FROM FILE USPATFULL

=> d iall hitstr

L52 ANSWER 1 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
 ACCESSION NUMBER: 2003:491200 HCAPLUS
 DOCUMENT NUMBER: 139:53022
 ENTRY DATE: Entered STN: 27 Jun 2003
 TITLE: Preparation of thiadiazoline derivatives as antitumor agents
 INVENTOR(S): Murakata, Chikara; Kato, Kazuhiko; Ohta, Yoshihisa; Nakai, Ryuichiro; Yamashita, Yoshinori; Takahashi, Takeshi; Nakano, Tomohisa; Ino, Yoji
 PATENT ASSIGNEE(S): Kyowa Hakko Kogyo Co., Ltd., Japan; Fuji Photo Film Co., Ltd.
 SOURCE: PCT Int. Appl., 154 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 INT. PATENT CLASSIF.:
 MAIN: C07D285-135
 SECONDARY: C07D417-04; C07D285-14; A61K031-433; A61K031-4439; A61K031-497; A61K031-5377; A61P035-00
 CLASSIFICATION: 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))
 Section cross-reference(s): 1, 63
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003051854	A1	20030626	WO 2002-JP12961	20021211
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,				

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
 PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
 UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
 KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
 FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ,
 CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1454903 A1 20040908 EP 2002-788786 20021211

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK

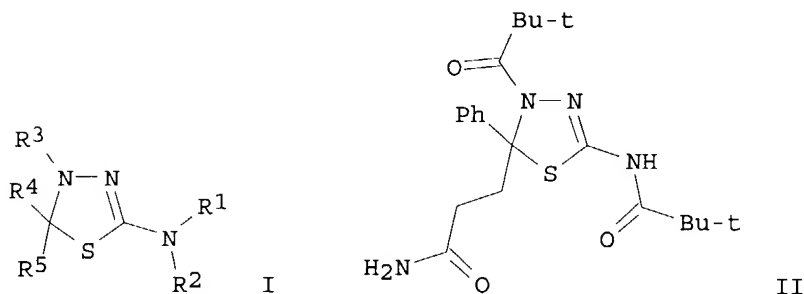
PRIORITY APPLN. INFO.: JP 2001-377456 A 20011211
 JP 2002-237399 A 20020816
 WO 2002-JP12961 W 20021211

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003051854	ICM	C07D285-135
	ICS	C07D417-04; C07D285-14; A61K031-433; A61K031-4439; A61K031-497; A61K031-5377; A61P035-00
EP 1454903	ECLA	A61K031/433; A61K031/4439; A61K031/497; A61K031/5377; C07D285/12D6D3

OTHER SOURCE(S): MARPAT 139:53022

GRAPHIC IMAGE:



ABSTRACT:

The title thiadiazoline derivs. with general formula of I [wherein R1 and R4 = independently H, (un)substituted alkyl, alkynyl, alkenyl, cycloalkyl, heterocyclyl, or aryl; R2 = H, (un)substituted alkyl, alkynyl, alkenyl, cycloalkyl, COR6, or CSR6; R6 = H, (un)substituted alkyl, alkenyl, cycloalkyl, aryl, heterocyclyl, amino, OH, SH, or SO2R7; R7 = (un)substituted alkyl, alkenyl, aryl, or heterocyclyl; or R1 and R2 together form an (un)substituted heterocycle with the nitrogen atom attached; R5 = (un)substituted alkyl, alkynyl, alkenyl, cycloalkyl, heterocyclyl, or aryl; or R4 and R5 together form an (un)substituted ring with the carbon atom attached; R3 = H, COR6, or CSR6] and pharmaceutically acceptable salts thereof are prepared as antitumor agents. For example, the compound II was prepared in a multi-step synthesis in moderate yield. II showed inhibitory activity with GI50 of 0.061 μ M against human large bowel cancer cell growth. Formulations containing I as an active ingredient were also described.

SUPPL. TERM: phenyl amino thiadiazoline antitumor agent prepn human
 formulation
 INDEX TERM: Antitumor agents
 Human
 Neoplasm
 (preparation of thiadiazoline derivs. as antitumor agents)

INDEX TERM: 72926-06-8P 72926-24-0P 332389-23-8P 433235-71-3P
 510764-26-8P 546110-44-5P 546110-53-6P 546110-55-8P
 546110-57-0P 546110-78-5P 546110-87-6P 546110-90-1P
 546111-01-7P 546111-04-0P 546111-07-3P 546111-11-9P
 546111-20-0P 546111-21-1P 546111-23-3P 546111-26-6P
 546111-27-7P 546111-35-7P 546111-36-8P 546111-39-1P
 546111-40-4P 546111-41-5P 546111-42-6P 546111-43-7P
 546111-44-8P 546111-46-0P 546111-49-3P 546111-64-2P
 546111-67-5P 546111-69-7P 546111-70-0P 546111-72-2P
 546111-74-4P 546111-76-6P 546111-78-8P 546111-79-9P
 546111-87-9P 546111-91-5P 546111-92-6P 546111-99-3P
 546112-01-0P 546112-06-5P 546112-07-6P 546112-11-2P
 546112-12-3P 546112-13-4P 546112-14-5P 546112-16-7P
 546112-18-9P 546112-19-0P
 ROLE: PAC (Pharmacological activity); RCT (Reactant); SPN
 (Synthetic preparation); THU (Therapeutic use); BIOL
 (Biological study); PREP (Preparation); RACT (Reactant or
 reagent); USES (Uses)
 (antitumor agent; preparation of thiadiazoline derivs. as
 antitumor agents)

INDEX TERM: 72926-23-9P 89992-30-3P 107261-68-7P 150007-07-1P
 150007-08-2P 150007-09-3P 332389-24-9P 333776-50-4P
 356773-12-1P 356773-13-2P 403518-07-0P 403518-08-1P
 443105-46-2P 443105-56-4P 443105-64-4P 443105-73-5P
 443105-83-7P 510717-71-2P 546110-41-2P 546110-42-3P
 546110-43-4P 546110-45-6P 546110-46-7P 546110-47-8P
 546110-48-9P 546110-49-0P 546110-50-3P 546110-51-4P
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 546111-85-7P 546111-86-8P 546111-88-0P 546111-89-1P
 546111-90-4P 546111-93-7P 546111-94-8P 546111-95-9P
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 546112-02-1P 546112-03-2P 546112-04-3P 546112-05-4P
 546112-08-7P 546112-09-8P 546112-10-1P 546112-15-6P
 546112-17-8P 546112-20-3P
 ROLE: PAC (Pharmacological activity); SPN (Synthetic
 preparation); THU (Therapeutic use); BIOL (Biological
 study); PREP (Preparation); USES (Uses)

(antitumor agent; preparation of thiadiazoline derivs. as antitumor agents)

INDEX TERM: 777-16-2P 1752-30-3P 2302-93-4P 3115-21-7P
 3689-17-6P 3766-55-0P 5351-71-3P 5351-77-9P
 5351-80-4P 5424-45-3P 6699-22-5P 6839-90-3P
 7410-54-0P 7420-37-3P 7441-53-4P 7651-47-0P
 13370-86-0P 13466-30-3P 14923-71-8P 16546-08-0P
 22233-81-4P 22397-20-2P 27421-65-4P 40104-24-3P
 41904-33-0P 54688-10-7P 56062-81-8P 65110-11-4P
 74227-66-0P 78597-06-5P 91994-49-9P 106010-23-5P
 132898-26-1P 132898-27-2P 132898-29-4P 133477-39-1P
 149634-41-3P 153736-25-5P 159793-04-1P 225644-99-5P
 316136-99-9P 331649-40-2P 340737-11-3P 387846-90-4P
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 387847-12-3P 499142-35-7P 546112-21-4P 546112-22-5P
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 546112-35-0P 546112-36-1P 546112-37-2P 546112-38-3P
 546112-39-4P 546112-40-7P 546112-41-8P 546112-42-9P
 546112-43-0P 546112-44-1P 546112-45-2P 546112-46-3P
 546112-47-4P 546112-48-5P 546112-49-6P 546112-50-9P
 546112-78-1P

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation of thiadiazoline derivs. as antitumor agents)

INDEX TERM: 57-06-7, Allyl isothiocyanate 67-64-1, Acetone, reactions
 79-19-6, Thiosemicarbazide 79-30-1, Isobutyryl chloride
 79-44-7, Dimethylcarbamoyle chloride 83-33-0, 1-Indanone
 88-15-3, 2-Acetylthiophene 89-74-7, 2',4'-
 Dimethylacetophenone 93-08-3, 2'-Acetonaphthone 93-55-0,
 Propiophenone 97-72-3, Isobutyric acid anhydride
 98-86-2, Acetophenone, reactions 99-02-5,
 3'-Chloroacetophenone 99-91-2, 4'-Chloroacetophenone
 99-93-4, 4'-Hydroxyacetophenone 100-06-1,
 4'-Methoxyacetophenone 100-19-6, 4'-Nitroacetophenone
 100-39-0, Benzyl bromide 100-83-4, 3-Hydroxybenzaldehyde
 106-31-0, Butyric acid anhydride 107-08-4, Propyl iodide
 108-91-8, Cyclohexylamine, reactions 108-94-1,
 Cyclohexanone, reactions 109-73-9, Butylamine, reactions
 109-83-1, 2-(Methylamino)ethanol 110-89-4, Piperidine,
 reactions 110-91-8, Morpholine, reactions 111-42-2,
 Diethanolamine, reactions 118-93-4, 2'-Hydroxyacetophenone
 119-61-9, Benzophenone, reactions 121-71-1,
 3'-Hydroxyacetophenone 121-89-1, 3'-Nitroacetophenone
 122-00-9, 4'-Methylacetophenone 122-57-6,
 Benzylideneacetone 123-62-6, Propionic acid anhydride
 142-61-0, Hexanoyl chloride 349-76-8, 3'-
 (Trifluoromethyl)acetophenone 350-03-8, 3-Acetylpyridine
 403-42-9, 4'-Fluoroacetophenone 445-27-2,
 2'-Fluoroacetophenone 455-36-7, 3'-Fluoroacetophenone
 497-38-1, 2-Norbornanone 502-56-7, 5-Nonanone 529-34-0,
 α -Tetralone 530-93-8, β -Tetralone 577-16-2,
 2'-Methylacetophenone 577-56-0, 2-Acetylbenzoic acid
 577-59-3, 2'-Nitroacetophenone 579-74-8,
 2'-Methoxyacetophenone 585-74-0, 3'-Methylacetophenone
 586-37-8, 3'-Methoxyacetophenone 591-78-6, 2-Hexanone
 611-70-1, Isopropyl phenyl ketone 616-30-8,
 3-Amino-1,2-propanediol 626-58-4, 4-Methylpiperidine

927-58-2, 4-Bromobutyryl chloride 936-59-4,
 3-Chloropropiophenone 941-98-0, 1'-Acetonaphthone
 1009-14-9, Butyl phenyl ketone 1072-83-9, 2-Acetylpyrrole
 1122-54-9, 4-Acetylpyridine 1122-62-9, 2-Acetylpyridine
 1192-62-7, 2-Acetylfuran 1197-09-7, 3',4'-
 Dihydroxyacetophenone 1443-80-7, 4-Acetylbenzonitrile
 1468-39-9, Isovaleric acid anhydride 1468-83-3,
 3-Acetylthiophene 1501-04-8, 4-(Carbomethoxy)butyrophenone
 1501-26-4 1579-15-3, 2-Acetoxy-1-indanone 2040-04-2,
 2',6'-Dimethoxyacetophenone 2142-68-9,
 2'-Chloroacetophenone 2142-69-0, 2'-Bromoacetophenone
 2550-26-7, Benzylacetone 3282-30-2, Pivaloyl chloride
 3481-02-5, Cyclopropyl phenyl ketone 3506-36-3,
 3-(Dimethylamino)propiofenone 4224-70-8, 6-Bromohexanoic
 acid 4346-94-5, Thiosemicarbazide monohydrochloride
 4509-90-4, 5-Bromovaleryl chloride 4524-93-0,
 Cyclopentylcarbonyl chloride 5370-25-2,
 1-(5-Bromo-2-thienyl)ethanone 5468-37-1,
 2-Aminoacetophenone hydrochloride 6136-68-1,
 3-Acetylbenzonitrile 6610-29-3, 4-Methylthiosemicarbazide
 10487-71-5, Crotonoyl chloride 13431-34-0,
 4-Ethylthiosemicarbazide 13679-72-6, 2-Acetyl-3-
 methylthiophene 16819-79-7 22047-25-2, Acetylpyrazine
 22720-75-8, 2-Acetylbenzothiofene 24295-03-2,
 2-Acetylthiazole 24424-99-5, Di-tert-butyl dicarbonate
 25333-24-8 26976-88-5 38870-89-2, Methoxyacetyl chloride
 40635-66-3, 2-Acetoxyisobutyryl chloride 42877-08-7,
 1-(3-Bromo-2-thienyl)ethanone 51863-60-6,
 3',5'-Dihydroxyacetophenone 80344-24-7 89581-82-8
 ROLE: RCT (Reactant); RACT (Reactant or reagent)

(preparation of thiadiazoline derivs. as antitumor agents)

REFERENCE COUNT:

19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS
 RECORD.

REFERENCE(S):

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 1989, V3(2), P119 HCAPLUS
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 Sciences 1990, V4(1), P77
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 P53 HCAPLUS
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- (13) Hassan, S; J Saudi Chem Soc 1999, V3(2), P171 HCAPLUS
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 Sciences 1989, V3(2), P221 HCAPLUS
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 HCAPLUS
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 HCAPLUS
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 Related Elements 1997, V122, P307
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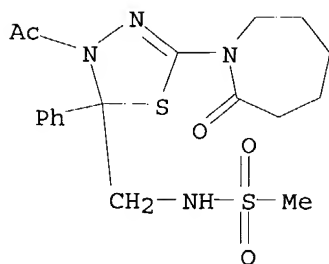
IT 546111-77-7P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
(Uses)

(antitumor agent; preparation of thiadiazoline derivs. as antitumor agents)

RN 546111-77-7 HCAPLUS

CN 1,3,4-Thiadiazole-2-methanamine, 3-acetyl-5-(hexahydro-2-oxo-1H-azepin-1-yl)-2,3-dihydro-N-(methylsulfonyl)-2-phenyl- (9CI) (CA INDEX NAME)



=> d iall hitstr 2-16

L52 ANSWER 2 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2001:502429 HCAPLUS

DOCUMENT NUMBER: 135:92553

ENTRY DATE: Entered STN: 12 Jul 2001

TITLE: Synthesis and activity of pyrroloazepine derivatives
as 5-HT antagonists

INVENTOR(S): Mizuno, Akira; Shibata, Makoto; Iwamori, Tomoe;
Shimamoto, Tetsuo; Nakanishi, Kyoko; Inomata, Norio

PATENT ASSIGNEE(S): Suntory Ltd., Japan

SOURCE: U.S., 54 pp., Cont.-in-part of U.S. Ser. No. 875,495.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

INT. PATENT CLASSIF.: A61K031-35; A61P007-00; A61P009-00

US PATENT CLASSIF.: 514215000

CLASSIFICATION: 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

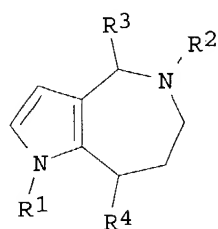
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6258805	B1	20010710	US 1999-312713	19990517
WO 9720845	A1	19970612	WO 1996-JP3522	19961202
W: AU, CA, HU, IL, JP, KR, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5962448	A	19991005	US 1997-875495	19970821
US 2002072515	A1	20020613	US 2001-801816	20010309
US 6489473	B2	20021203		
US 2003166926	A1	20030904	US 2002-188234	20020703
US 6713634	B2	20040330		
PRIORITY APPLN. INFO.:			JP 1995-335714	A 19951201
			JP 1996-46928	A 19960209
			WO 1996-JP3522	W 19961202
			US 1997-875495	A2 19970821
			US 1999-312713	A1 19990517

US 2001-801816

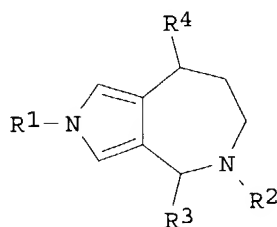
A1 20010309

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 6258805	IC	A61K031-35IC A61P007-00IC A61P009-00
	NCL	514215000
US 2002072515	ECLA	C07D207/34; C07D487/04; C07D495/20
US 2003166926	ECLA	C07D207/34; C07D487/04; C07D495/20
OTHER SOURCE(S):		MARPAT 135:92553
GRAPHIC IMAGE:		



I



II

ABSTRACT:

Synthesis of pyrroloazepine derivs. (I) and (II) [R1 = H, alkyl, Ph, benzyl; R2 = substituted alkyl; R3,R4 independently = =O, =NOH, OH, OMe, SCH2CH2S] or pharmaceutically acceptable salts for use as 5-HT antagonists is disclosed. Thus, I (R1 = Me, R2 = (CH2)2-piperazinyl-C6H4F, R3 = =O, R4 = OH) (III) was prepared by condensation of 3-pyrrolicarboxylic acid with β -alanine Et ester hydrochloride, the amide ester saponified and the acid cyclized to pyrroloazepine with polyphosphoric acid, the azepine N alkylated with bromoalkylchloride followed by 1-(4-fluorophenyl)piperazine and reduction of carbonyl with NaBH4. III shows a 90.2% contraction at 10-7M in 5-HT action assay. I and II have strong serotonin-2 receptor antagonistic action and low toxicity and less side effects, and are therapeutically useful in the treatment of circulatory diseases and/or conditions related thereto.

SUPPL. TERM: pyrroloazepine alkyl prepn 5HT antagonists; antihypotensive circulatory disease alkylpyrroloazepine

INDEX TERM: Circulation
(disorder, treatment; synthesis and activity of pyrroloazepine derivs. as 5-HT antagonists)

INDEX TERM: 5-HT antagonists
Antihypotensives
(synthesis and activity of pyrroloazepine derivs. as 5-HT antagonists)

INDEX TERM: 191592-35-5P 191592-36-6P
ROLE: BAC (Biological activity or effector, except adverse);
BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(synthesis and activity of pyrroloazepine derivs. as 5-HT antagonists)

INDEX TERM: 191591-53-4P 191591-54-5P 191591-55-6P 191591-56-7P
191591-57-8P 191591-58-9P 191591-59-0P 191591-60-3P
191591-61-4P 191591-62-5P 191591-63-6P 191591-64-7P

191591-66-9P 191591-67-0P 191591-68-1P 191591-69-2P
 191591-70-5P 191591-71-6P 191591-72-7P 191591-73-8P
 191591-74-9P 191591-75-0P 191591-77-2P 191591-78-3P
 191591-80-7P 191591-82-9P 191591-83-0P 191591-84-1P
 191591-85-2P 191591-86-3P 191591-87-4P 191591-88-5P
 191591-89-6P 191591-90-9P 191591-91-0P 191591-92-1P
 191591-93-2P 191591-94-3P 191591-95-4P 191591-96-5P
 191591-97-6P 191591-98-7P 191591-99-8P 191592-00-4P
 191592-01-5P 191592-02-6P 191592-03-7P 191592-09-3P
 191592-27-5P 191592-30-0P 282550-40-7P

ROLE: BAC (Biological activity or effector, except adverse);
 BSU (Biological study, unclassified); RCT (Reactant); SPN
 (Synthetic preparation); THU (Therapeutic use); BIOL
 (Biological study); PREP (Preparation); RACT (Reactant or
 reagent); USES (Uses)

(synthesis and activity of pyrroloazepine derivs. as 5-HT
 antagonists)

INDEX TERM:

191591-65-8P 191591-81-8P 191592-04-8P
191592-05-9P 191592-06-0P 191592-08-2P
 191592-10-6P 191592-11-7P 191592-12-8P 191592-13-9P
 191592-14-0P 191592-15-1P 191592-16-2P 191592-17-3P
 191592-18-4P 191592-19-5P 191592-20-8P 191592-21-9P
 191592-22-0P 191592-23-1P 191592-24-2P 191592-26-4P
 191592-28-6P 191592-29-7P 191592-31-1P 191593-28-9P
 191593-29-0P 282550-39-4P 349083-22-3P 349083-23-4P

ROLE: BAC (Biological activity or effector, except adverse);
 BSU (Biological study, unclassified); SPN (Synthetic
 preparation); THU (Therapeutic use); BIOL (Biological
 study); PREP (Preparation); USES (Uses)

(synthesis and activity of pyrroloazepine derivs. as 5-HT
 antagonists)

INDEX TERM:

92-54-6, 1-Phenylpiperazine 109-70-6, 1-Bromo-3-
 chloropropane 540-63-6, 1,2-Ethanedithiol 623-47-2,
 Ethyl propiolate 771-99-3, 4-Phenylpiperidine 841-77-0,
 1-Diphenylmethylpiperazine 922-67-8, Methyl propiolate
 931-03-3, 3-Pyrrolicarboxylic acid 1011-16-1,
 1-(2-Fluorophenyl)piperazine hydrochloride 2252-63-3
 2262-12-6 4244-84-2, β -Alanine ethyl ester
 hydrochloride 5470-11-1, Hydroxylamine hydrochloride
 6269-89-2, 1-(4-Nitrophenyl)piperazine 13078-12-1
 27019-47-2, β -Alanine benzyl ester p-toluenesulfonate
 38456-66-5, N-Formylsarcosine 38869-47-5,
 1-(4-Methoxyphenyl)piperazine dihydrochloride 57238-81-0
 64276-66-0, 4-Methyl-3-Pyrrolicarboxylic acid 65274-89-7
 68384-82-7 78158-74-4 79144-84-6 84163-77-9
 86731-89-7 94021-22-4, 1-(2-Pyrimidinyl)piperazine
 dihydrochloride 191592-38-8

ROLE: RCT (Reactant); RACT (Reactant or reagent)

(synthesis and activity of pyrroloazepine derivs. as 5-HT
 antagonists)

INDEX TERM:

36929-61-0P 40611-74-3P 99972-42-6P 128259-47-2P
 190582-35-5P 191592-37-7P 282550-44-1P 345203-93-2P

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP
 (Preparation); RACT (Reactant or reagent)

(synthesis and activity of pyrroloazepine derivs. as 5-HT
 antagonists)

REFERENCE COUNT:

6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS
 RECORD.

REFERENCE(S):

- (1) Imoto; US 5684161 1997 HCAPLUS
- (2) Mizuno; US 5206239 1993 HCAPLUS

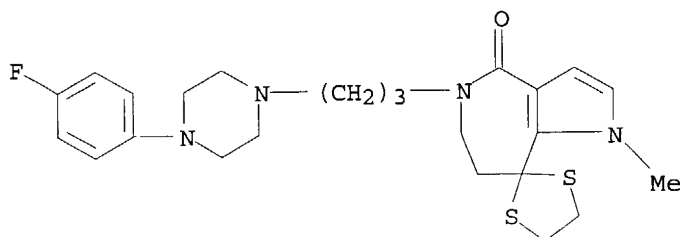
- (3) Mizuno; US 5391731 1995 HCAPLUS
 (4) Mizuno; US 5397780 1995 HCAPLUS
 (5) Mizuno; US 5399557 1995 HCAPLUS
 (6) Mizuno; US 5416082 1995 HCAPLUS

IT 191592-05-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (synthesis and activity of pyrroloazepine derivs. as 5-HT antagonists)

RN 191592-05-9 HCAPLUS

CN Spiro[1,3-dithiolane-2,8'-(1'H)-pyrrolo[3,2-c]azepin]-4'-(5'H)-one,
 5'-[3-[4-(4-fluorophenyl)-1-piperazinyl]propyl]-6',7'-dihydro-1'-methyl-
 (9CI) (CA INDEX NAME)



L52 ANSWER 3 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 1997:461620 HCAPLUS

DOCUMENT NUMBER: 127:81465

ENTRY DATE: Entered STN: 24 Jul 1997

TITLE: Preparation of pyrroloazepine derivatives as serotonin-2 receptor antagonists

INVENTOR(S): Mizuno, Akira; Shibata, Makoto; Iwamori, Tomoe; Shimamoto, Tetsuo; Nakanishi, Kyoko; Inomata, Norio

PATENT ASSIGNEE(S): Suntory Limited, Japan

SOURCE: PCT Int. Appl., 160 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

INT. PATENT CLASSIF.:

MAIN: C07D487-04

SECONDARY: A61K031-55

CLASSIFICATION: 28-17 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9720845	A1	19970612	WO 1996-JP3522	19961202
W: AU, CA, HU, IL, JP, KR, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2212092	AA	19970612	CA 1996-2212092	19961202
AU 9676558	A1	19970627	AU 1996-76558	19961202
AU 719230	B2	20000504		
EP 807632	A1	19971119	EP 1996-939340	19961202
EP 807632	B1	20020417		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, FI

IL 121432	A1	20000928	IL 1996-121432	19961202
AT 216388	E	20020515	AT 1996-939340	19961202
ES 2179218	T3	20030116	ES 1996-939340	19961202
JP 3563076	B2	20040908	JP 1997-521152	19961202
US 5962448	A	19991005	US 1997-875495	19970821
US 6258805	B1	20010710	US 1999-312713	19990517
US 2002072515	A1	20020613	US 2001-801816	20010309
US 6489473	B2	20021203		
US 2003166926	A1	20030904	US 2002-188234	20020703
US 6713634	B2	20040330		
PRIORITY APPLN. INFO.:			JP 1995-335714	A 19951201
			JP 1996-46928	A 19960209
			WO 1996-JP3522	W 19961202
			US 1997-875495	A2 19970821
			US 1999-312713	A1 19990517
			US 2001-801816	A1 20010309

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9720845	ICM	C07D487-04
	ICS	A61K031-55
US 2002072515	ECLA	C07D207/34; C07D487/04; C07D495/20
US 2003166926	ECLA	C07D207/34; C07D487/04; C07D495/20
OTHER SOURCE(S):		MARPAT 127:81465
GRAPHIC IMAGE:		

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

ABSTRACT:

The title compds. [I; ring P = (un)substituted pyrrole ring; A = alkylene, alkenylene, alkynylene; Y = N-containing heterocyclyl, etc; Z1, E2 = H, lower alkyl; dotted line = bond or none] are prepared I, having a potent serotonin-2 receptor antagonism, are reduced in toxicity and side effects, and are useful as therapeutic agents for circulatory diseases such as ischemic heart diseases, cerebrovascular disorders, and peripheral circulatory disturbances. Thus, pyrroloazepine derivative (II) (preparation given) was reacted with HSCH₂CH₂SH in the presence of BF₃.Et₂O in AcOH to give 79% the title compound (III), which at 10⁻⁸ M showed 75.5% inhibitory activity against serotonin (5-HT).

SUPPL. TERM: pyrroloazepine prepn serotonin receptor antagonist;
 circulatory disease treatment pyrroloazepine prepn; ischemic heart disease treatment pyrroloazepine prepn;
 cerebrovascular disorder treatment pyrroloazepine prepn;
 peripheral circulatory disturbance treatment pyrroloazepine prepn

INDEX TERM: Brain, disease
 (cerebrovascular; preparation of pyrroloazepine derivs. as therapeutic agents for circulatory diseases such as ischemic heart diseases, cerebrovascular disorders, and peripheral circulatory disturbances)

INDEX TERM: 5-HT receptors
 Tumor necrosis factors
 ROLE: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)

(preparation of pyrroloazepine derivs. as serotonin-2 receptor antagonists)

INDEX TERM: Heart, disease

(preparation of pyrroloazepine derivs. as therapeutic agents for circulatory diseases such as ischemic heart diseases, cerebrovascular disorders, and peripheral circulatory disturbances)

INDEX TERM: 191591-53-4P 191591-54-5P 191591-55-6P 191591-56-7P
 191591-57-8P 191591-58-9P 191591-59-0P 191591-60-3P
 191591-61-4P 191591-62-5P 191591-63-6P 191591-64-7P
 191591-65-8P 191591-66-9P 191591-67-0P 191591-68-1P
 191591-69-2P 191591-70-5P 191591-71-6P 191591-72-7P
 191591-73-8P 191591-74-9P 191591-75-0P 191591-76-1P
 191591-77-2P 191591-78-3P 191591-80-7P 191591-81-8P
 191591-82-9P 191591-83-0P 191591-84-1P 191591-85-2P
 191591-86-3P 191591-87-4P 191591-88-5P 191591-89-6P
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 191592-25-3P 191592-26-4P 191592-27-5P 191592-28-6P
 191592-29-7P 191592-30-0P 191592-31-1P 191592-32-2P
 191592-33-3P 191592-34-4P 191592-35-5P 191592-36-6P
 191593-28-9P 191593-29-0P

ROLE: BAC (Biological activity or effector, except adverse);
 BSU (Biological study, unclassified); SPN (Synthetic
 preparation); THU (Therapeutic use); BIOL (Biological
 study); PREP (Preparation); USES (Uses)

(preparation of pyrroloazepine derivs. as serotonin-2 receptor antagonists)

INDEX TERM: 74-88-4, Methyl iodide, reactions 92-54-6,
 1-Phenylpiperazine 100-39-0, Benzyl bromide 101-83-7,
 Dicyclohexylamine 105-37-3, Ethyl propanoate 109-70-6,
 1-Bromo-3-chloropropane 540-63-6, 1,2-Ethanedithiol
 554-12-1, Methyl propanoate 771-99-3, 4-Phenylpiperidine
 841-77-0, 1-Diphenylmethylpiperazine 1011-16-1,
 1-(2-Fluorophenyl)piperazine hydrochloride 2252-63-3,
 1-(4-Fluorophenyl)piperazine 2262-12-6 4244-84-2,
 β -Alanine ethyl ester hydrochloride 6269-89-2,
 1-(4-Nitrophenyl)piperazine 6652-06-8 6940-78-9,
 1-Bromo-4-chlorobutane 13078-12-1 25519-78-2,
 4-(4-Fluorobenzoyl)piperidine hydrochloride 38456-66-5,
 N-Formylsarcosine 38869-47-5, 1-(4-Methoxyphenyl)piperazine dihydrochloride 42854-62-6
 65274-89-7 78158-74-4 79144-84-6 84163-68-8
 86731-89-7 94021-22-4, 1-(2-Pyrimidinyl)piperazine
 dihydrochloride 191592-38-8

ROLE: RCT (Reactant); RACT (Reactant or reagent)

(preparation of pyrroloazepine derivs. as serotonin-2 receptor antagonists)

INDEX TERM: 36929-61-0P 40611-74-3P 99972-42-6P 128259-47-2P
 190582-35-5P 191592-37-7P

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP
 (Preparation); RACT (Reactant or reagent)

(preparation of pyrroloazepine derivs. as serotonin-2 receptor

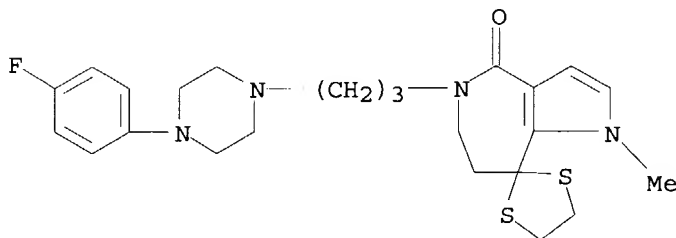
antagonists)

IT 191592-05-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrroloazepine derivs. as serotonin-2 receptor antagonists)

RN 191592-05-9 HCAPLUS

CN Spiro[1,3-dithiolane-2,8'-(1'H)-pyrrolo[3,2-c]azepin]-4'-(5'H)-one,
5'-[3-[4-(4-fluorophenyl)-1-piperazinyl]propyl]-6',7'-dihydro-1'-methyl-
(9CI) (CA INDEX NAME)



L52 ANSWER 4 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 4

ACCESSION NUMBER: 1997:640247 HCAPLUS

DOCUMENT NUMBER: 127:318890

ENTRY DATE: Entered STN: 09 Oct 1997

TITLE: Benzo-fused lactams promoting release of growth hormone

INVENTOR(S): Wyvratt, Matthew; Devita, Robert; Bochis, Richard; Schoen, William

PATENT ASSIGNEE(S): Merck and Co., Inc., USA

SOURCE: U.S., 76 pp., Cont.-in-part of U.S. 5,283,241.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

INT. PATENT CLASSIF.:

MAIN: A61K031-55

SECONDARY: C07D209-34; C07D215-227; C07D223-16

US PATENT CLASSIF.: 514183000

CLASSIFICATION: 27-21 (Heterocyclic Compounds (One Hetero Atom))

Section cross-reference(s): 1, 2, 17, 63

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5672596	A	19970930	US 1995-392961	19950418
US 5283241	A	19940201	US 1992-936975	19920828
WO 9405634	A1	19940317	WO 1993-US7791	19930818
W: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5968924	A	19991019	US 1997-820302	19970318
PRIORITY APPLN. INFO.:			US 1992-936975	A2 19920828
			WO 1993-US7791	W 19930818
			US 1995-392961	A3 19950418

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 5672596	ICM	A61K031-55
	ICS	C07D209-34; C07D215-227; C07D223-16
	NCL	514183000

OTHER SOURCE(S): MARPAT 127:318890

GRAPHIC IMAGE:

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

ABSTRACT:

There are disclosed certain novel benzo-fused lactams I [Ar = (un)substituted Ph; L = (un)substituted C₆H₄; m = 0, 1; p = 0-3; q = 0-4; X = bond, CO, O, S, S(O), S(O)₂, CH(OH), (un)substituted NH, CH:CH; R₁, R₂ = H, halo, alkyl, perfluoroalkyl, cyano, NO₂, (un)substituted Ph, etc.; R₄, R₅ = (un)substituted alk(en/yn)yl or Ph; or R₄R₅ = alkylene chain with optional heteroat. interruptions; R₆ = H, alkyl, Ph, or phenylalkyl; A = alkylene chain with optional substituents or spirocyclic alkylene fusion]. The compds. promote the release of growth hormone in humans and animals (no data). This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to increase the stature of those afflicted with a lack of a normal secretion of natural growth hormone. Growth promoting compns. containing I as active ingredients are also disclosed. Approx. 60 synthetic examples with characterizing phys. data are given. For instance, amidation of 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one with 3-[(tert-butoxycarbonyl)amino]-3-methylbutanoic acid (prepns. given) using the reagents BOP and Et₃N (94%), followed by N-alkylation in the 1-position with 4-(bromomethyl)-2'-[(methoxycarbonyl)amino]-1,1'-biphenyl using NaH in DMF (63%), and deprotection with CF₃CO₂H (96%), gave title compound II as the trifluoroacetate salt.

SUPPL. TERM: benzo lactam growth hormone release promoter; benzazepine
prepn growth hormone release promoter

INDEX TERM: Antiobesity agents
(preparation of benzo-fused lactams as growth hormone release
promoters)

INDEX TERM: Growth factors, animal
ROLE: AGR (Agricultural use); BAC (Biological activity or
effector, except adverse); BPR (Biological process); BSU
(Biological study, unclassified); MFM (Metabolic formation);
MSC (Miscellaneous); SPN (Synthetic preparation); THU
(Therapeutic use); BIOL (Biological study); FORM (Formation,
nonpreparative); PREP (Preparation); PROC (Process); USES
(Uses)
(preparation of benzo-fused lactams as growth hormone release
promoters)

INDEX TERM: Osteoporosis
(therapeutic agents; preparation of benzo-fused lactams as
growth hormone release promoters)

INDEX TERM: Adrenoceptor agonists
(α 2-, compns. containing; preparation of benzo-fused lactams
as growth hormone release promoters)

INDEX TERM: Adrenoceptor agonists
(β 3-, compns. containing; preparation of benzo-fused lactams
as growth hormone release promoters)

INDEX TERM: 114343-29-2P 169188-17-4P, 2'-Nitro-1,1'-biphenyl-4-
carboxaldehyde

ROLE: BYP (Byproduct); PREP (Preparation)
(byproduct; preparation of benzo-fused lactams as growth hormone release promoters)

INDEX TERM: 32980-26-0P, 2,2-Dimethylbutanedioic acid 1-methyl ester
160278-46-6P 197652-82-7P, 4-(Dibromomethyl)-2'-nitro-1,1'-biphenyl

ROLE: BYP (Byproduct); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(byproduct; preparation of benzo-fused lactams as growth hormone release promoters)

INDEX TERM: 9002-64-6, Parathyroid hormone 9034-39-3, Somatoliberin
15477-76-6D, Phosphonate, derivs. 36085-73-1, B-HT 920
67763-96-6, IGF-1 67763-97-7, IGF-2 87616-84-0
141925-59-9, GHRP-1 158861-67-7, GHRP-2

ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. containing; preparation of benzo-fused lactams as growth hormone release promoters)

INDEX TERM: 937-12-2P, (4-Methylphenyl)trimethylstannane 3349-64-2P, 1-Tetralone oxime 4424-80-0P, 2,3,4,5-Tetrahydro-1H-1-benzazepin-2-one 4879-95-2P, 4,4-Dimethylazetidin-2-one 16927-79-0P 51219-55-7P, 3-[[[(Benzyloxy)carbonyl]amino]-3-methylbutanoic acid 54043-71-9P, 2,2-Dimethylbutanedioic acid 4-methyl ester 70680-21-6P, 4-Methyl-2'-nitro-1,1'-biphenyl 86499-35-6P, 3-Amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one 101043-55-4P, 4-Methyl-2'-hydroxy-1,1'-biphenyl 114772-39-3P, 4-(Bromomethyl)-2'-nitro-1,1'-biphenyl 114772-53-1P, 4'-Methyl-1,1'-biphenyl-2-carbonitrile 128182-82-1P, 3-[[[(Benzyloxy)carbonyl]amino]-3-methylbutanoic acid methyl ester 129765-95-3P, 3-[(tert-Butoxycarbonyl)amino]-3-methylbutanoic acid 133776-42-8P, 4-Bromobenzyl tert-butyldiphenylsilyl ether 135689-84-8P, 3'-Bromo-4'-methyl-1,1'-biphenyl-2-carbonitrile 135689-85-9P, 3'-Bromo-4'-(bromomethyl)-1,1'-biphenyl-2-carbonitrile 137036-55-6P, (R)-3-Amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one 140700-64-7P, 3-Iodo-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one 145457-70-1P 145485-03-6P 145485-77-4P 145486-16-4P 145486-21-1P, 4-Methyl-2'-acetoxy-1,1'-biphenyl 145486-22-2P, 4-(Bromomethyl)-2'-acetoxy-1,1'-biphenyl 145486-23-3P 145486-24-4P, 4-Methyl-2'-(4-nitrophenoxy)-1,1'-biphenyl 145486-25-5P, 4-(Bromomethyl)-2'-(4-nitrophenoxy)-1,1'-biphenyl 145486-26-6P 145486-32-4P 145486-33-5P 145486-45-9P 145486-47-1P 145486-75-5P 148289-82-1P, [4-[[[(tert-Butyldiphenylsilyl)oxymethyl]phenyl]boronic acid 155300-46-2P, N-(tert-Butoxycarbonyl)-4,4-dimethylazetidin-2-one 159815-76-6P, 4-(Hydroxymethyl)-2'-nitro-1,1'-biphenyl 159815-77-7P 159815-78-8P 159815-79-9P 159815-80-2P 159815-81-3P 159815-82-4P 159815-83-5P 159815-84-6P 159815-85-7P 159815-86-8P 159815-87-9P 159815-88-0P 159815-89-1P 159815-90-4P 159815-92-6P 159815-93-7P 159815-95-9P 159815-96-0P 159815-97-1P, 4-Methyl-2'-(2-nitrophenoxy)-1,1'-biphenyl 159815-98-2P, 4-(Bromomethyl)-2'-(2-nitrophenoxy)-1,1'-biphenyl 159815-99-3P 159816-01-0P 160278-26-2P 162356-90-3P, N-(tert-Butoxycarbonyl)-2-bromobenzylamine 162356-92-5P 162356-93-6P 168059-24-3P 169188-18-5P 195248-05-6P 195248-06-7P 195248-07-8P 195248-08-9P 197652-11-2P 197652-13-4P 197652-15-6P 197652-17-8P

197652-19-0P 197652-21-4P 197652-23-6P 197652-25-8P
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 197652-35-0P 197652-38-3P 197652-40-7P 197652-41-8P
 197652-42-9P 197652-43-0P 197652-44-1P 197652-45-2P
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 3'-Bromo-4'-(acetoxymethyl)-1,1'-biphenyl-2-carbonitrile
 197652-49-6P, 3'-Bromo-4'-(hydroxymethyl)-1,1'-biphenyl-2-
 carbonitrile 197652-50-9P 197652-51-0P 197652-52-1P
 197652-53-2P 197652-54-3P 197652-55-4P 197652-56-5P
 197652-57-6P 197652-58-7P 197652-59-8P,
 2'-(2-Aminoethyl)-1,1'-biphenyl-4-methanol 197652-60-1P
 197652-61-2P 197652-62-3P 197652-63-4P 197652-64-5P
 197652-65-6P 197652-66-7P 197652-67-8P 197652-68-9P
 197652-69-0P 197652-70-3P 197652-71-4P 197652-73-6P
 197652-74-7P 197652-75-8P 197652-76-9P 197652-77-0P
 197652-78-1P 197652-79-2P 197652-80-5P

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP
 (Preparation); RACT (Reactant or reagent)

(intermediate; preparation of benzo-fused lactams as growth
 hormone release promoters)

INDEX TERM:

7727-37-9, Nitrogen, biological studies

ROLE: BPR (Biological process); BSU (Biological study,
 unclassified); BIOL (Biological study); PROC (Process)

(metabolism; treatment of nitrogen wasting; preparation of
 benzo-fused lactams as growth hormone release promoters)

INDEX TERM:

159814-84-3P 159814-90-1P 159814-92-3P 159814-96-7P

ROLE: AGR (Agricultural use); BAC (Biological activity or
 effector, except adverse); BSU (Biological study,
 unclassified); RCT (Reactant); SPN (Synthetic preparation);

THU (Therapeutic use); BIOL (Biological study); PREP
 (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of benzo-fused lactams as growth hormone release
 promoters)

INDEX TERM:

159814-82-1P 159814-86-5P 159814-88-7P 159814-94-5P
 159815-00-6P 159815-04-0P 159815-06-2P 159815-08-4P
 159815-10-8P 159815-12-0P 159815-14-2P 159815-16-4P
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 159815-26-6P 159815-28-8P 159815-30-2P 159815-32-4P
 159815-34-6P 159815-36-8P 159815-38-0P 159815-40-4P
 159815-42-6P 159815-44-8P 195248-02-3P 197650-26-3P
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 197650-45-6P 197650-48-9P 197650-49-0P 197650-50-3P
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 197650-75-2P 197650-76-3P 197650-77-4P 197650-79-6P
 197650-82-1P 197650-85-4P 197650-88-7P 197650-91-2P
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 197651-67-5P 197651-71-1P **197651-74-4P**
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197651-87-9P 197651-89-1P 197651-91-5P
 197651-93-7P 197651-96-0P 197651-98-2P 197652-00-9P
 197652-02-1P 197652-04-3P 197652-06-5P 197652-08-7P
 ROLE: AGR (Agricultural use); BAC (Biological activity or
 effector, except adverse); BSU (Biological study,
 unclassified); SPN (Synthetic preparation); THU (Therapeutic
 use); BIOL (Biological study); PREP (Preparation); USES
 (Uses)

(preparation of benzo-fused lactams as growth hormone release
 promoters)

INDEX TERM:

9002-72-6, Growth hormone

ROLE: BPR (Biological process); BSU (Biological study,
 unclassified); MFM (Metabolic formation); MSC
 (Miscellaneous); BIOL (Biological study); FORM (Formation,
 nonpreparative); PROC (Process)

(preparation of benzo-fused lactams as growth hormone release
 promoters)

INDEX TERM:

62-53-3, Benzenamine, reactions 100-46-9, Benzylamine,
 reactions 110-78-1, 1-Propyl isocyanate 110-85-0,
 Piperazine, reactions 110-91-8, Morpholine, reactions
 115-11-7, Isobutylene, reactions 350-46-9,
 1-Fluoro-4-nitrobenzene 529-34-0, 1-Tetralone 577-19-5,
 2-Bromo-1-nitrobenzene 597-43-3, 2,2-Dimethylsuccinic acid
 623-33-6, Glycine ethyl ester hydrochloride 700-87-8,
 2-Methoxyphenyl isocyanate 873-75-6, 4-Bromobenzyl alcohol
 1189-71-5, Chlorosulfonyl isocyanate 1493-27-2,
 1-Fluoro-2-nitrobenzene 1795-48-8, Isopropyl isocyanate
 2042-37-7, 2-Bromobenzonitrile 2142-69-0,
 2'-Bromoacetophenone 2462-31-9, Glycine benzyl ester
 hydrochloride 3173-56-6, Benzyl isocyanate 4294-57-9,
 p-Tolylmagnesium bromide 5465-63-4, 2-Bromobenzylamine
 hydrochloride 5720-05-8, 4-Tolylboronic acid 13139-17-8,
 N-[(Benzyloxy)carbonyloxy]succinimide 15030-72-5,
 N-(Carbobenzyloxy)-2-methylalanine 15159-40-7,
 4-Morpholinocarbonyl chloride 15186-48-8, D-Glyceraldehyde
 acetone 19472-74-3, 2-Bromophenylacetonitrile
 27532-96-3, Glycine tert-butyl ester hydrochloride
 30674-80-7 30992-29-1, N-(tert-Butoxycarbonyl)-2-
 methylalanine 81445-45-6, (R)-2-Benzyloxypropanal
 87037-69-2, (R)-2-Benzyloxy-1-propanol 96289-09-7
 114772-54-2, 4'-(Bromomethyl)-1,1'-biphenyl-2-carbonitrile
 197652-81-6

ROLE: RCT (Reactant); RACT (Reactant or reagent)

(starting material; preparation of benzo-fused lactams as
 growth hormone release promoters)

IT 197651-01-7P 197651-05-1P 197651-09-5P
 197651-13-1P 197651-17-5P 197651-22-2P
 197651-27-7P 197651-32-4P 197651-36-8P
 197651-41-5P 197651-47-1P 197651-52-8P

197651-56-2P 197651-61-9P 197651-74-4P

197651-87-9P

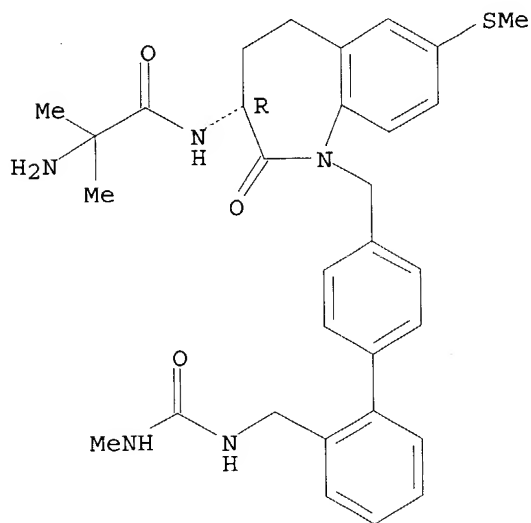
RL: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of benzo-fused lactams as growth hormone release promoters)

RN 197651-01-7 HCAPLUS

CN Propanamide, 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[(methylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, (R)- (9CI) (CA INDEX NAME)

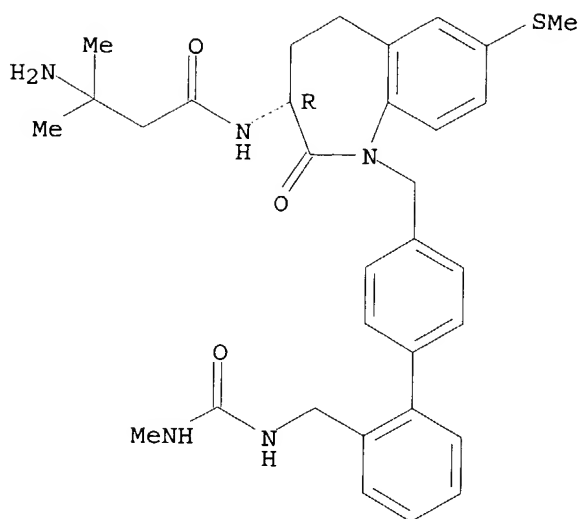
Absolute stereochemistry.



RN 197651-05-1 HCAPLUS

CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[(methylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, (R)- (9CI) (CA INDEX NAME)

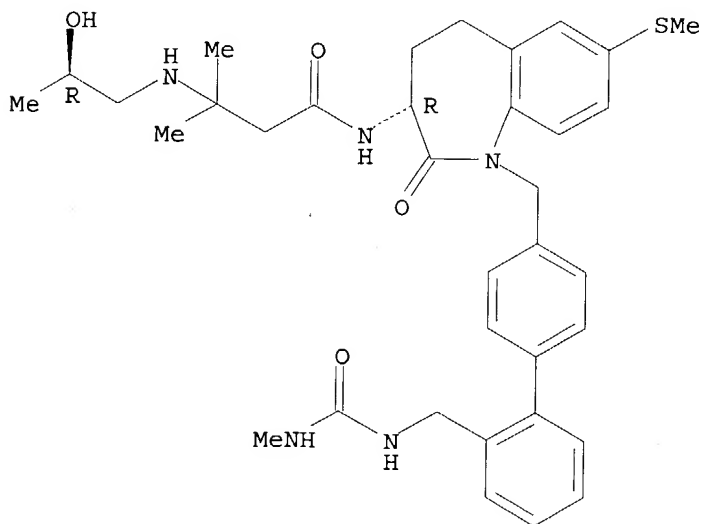
Absolute stereochemistry.



RN 197651-09-5 HCAPLUS

CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[(methylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

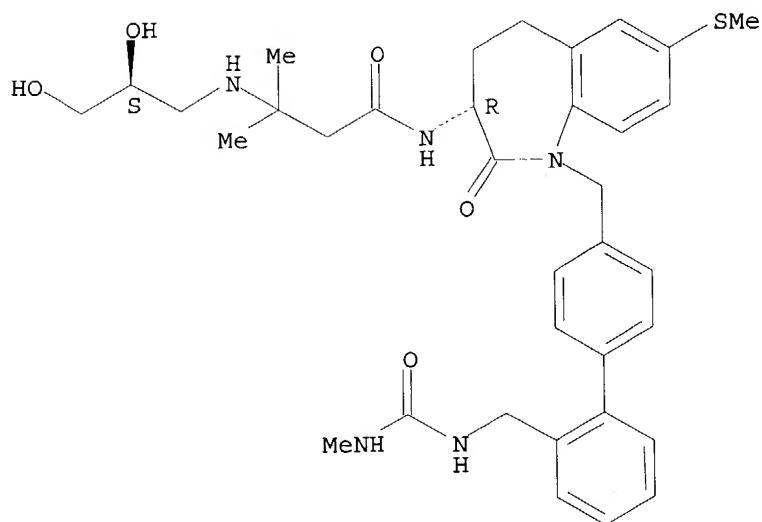
Absolute stereochemistry.



RN 197651-13-1 HCAPLUS

CN Butanamide, 3-[(2,3-dihydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[(methylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

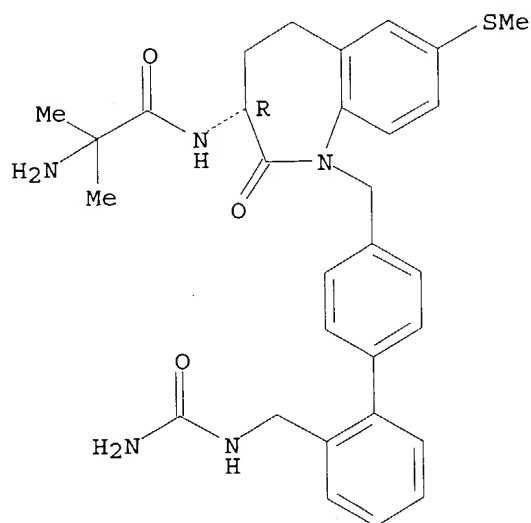
Absolute stereochemistry.



RN 197651-17-5 HCAPLUS

CN Propanamide, 2-amino-N-[1-[[2'-[[[(aminocarbonyl)amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-2-methyl-, (R)- (9CI) (CA INDEX NAME)

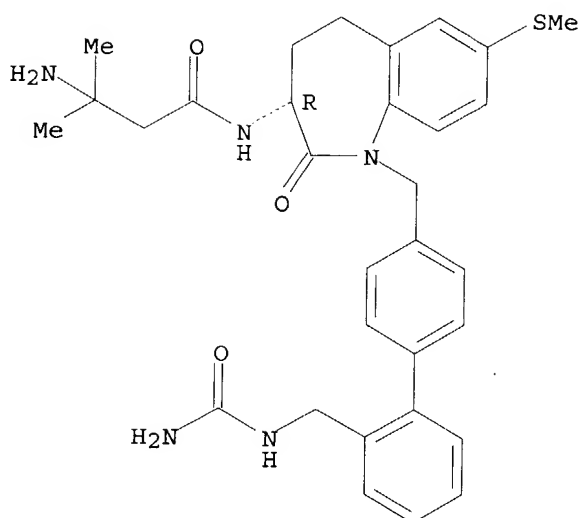
Absolute stereochemistry.



RN 197651-22-2 HCAPLUS

CN Butanamide, 3-amino-N-[1-[[2'-[[[(aminocarbonyl)amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-methyl-, (R)- (9CI) (CA INDEX NAME)

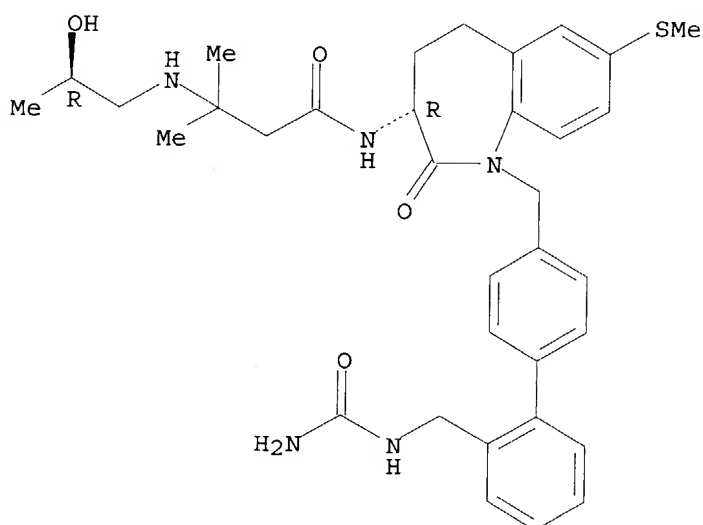
Absolute stereochemistry.



RN 197651-27-7 HCAPLUS

CN Butanamide, N-[1-[[2'-[[[(aminocarbonyl)amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-[(2-hydroxypropyl)amino]-3-methyl-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

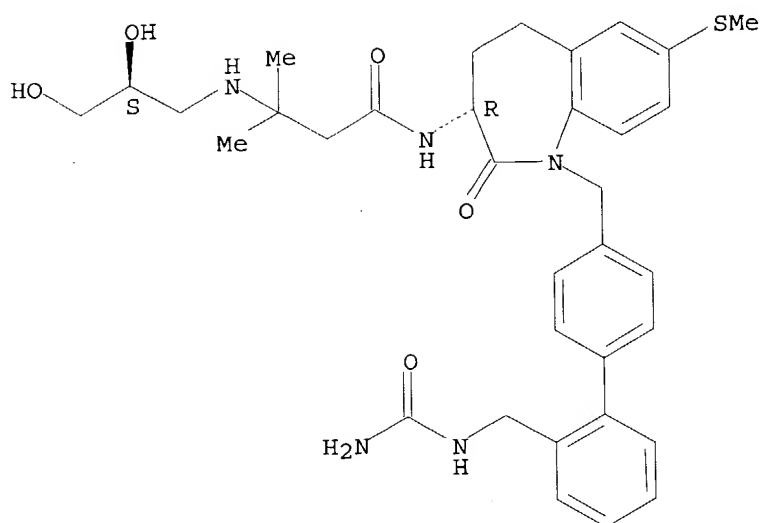
Absolute stereochemistry.



RN 197651-32-4 HCAPLUS

CN Butanamide, N-[1-[[2'-[[[(aminocarbonyl)amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-[(2,3-dihydroxypropyl)amino]-3-methyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

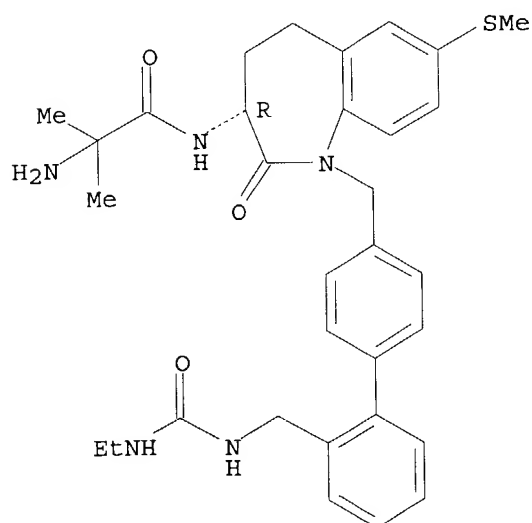
Absolute stereochemistry.



RN 197651-36-8 HCAPLUS

CN Propanamide, 2-amino-N-[1-[[2'-[[[(ethylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-2-methyl-, (R)- (9CI) (CA INDEX NAME)

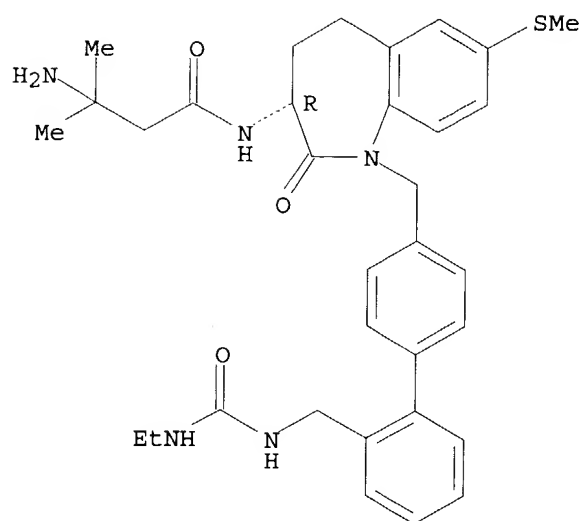
Absolute stereochemistry.



RN 197651-41-5 HCAPLUS

CN Butanamide, 3-amino-N-[1-[[2'-[[[(ethylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-methyl-, (R)- (9CI) (CA INDEX NAME)

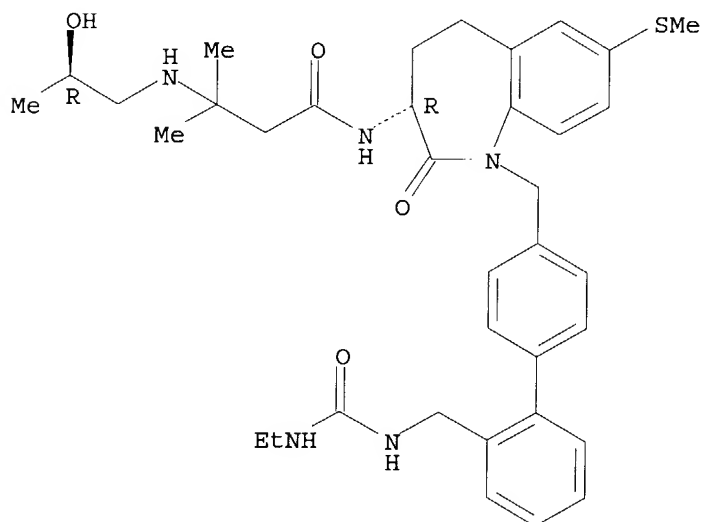
Absolute stereochemistry.



RN 197651-47-1 HCAPLUS

CN Butanamide, N-[1-[[2'-[[[(ethylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-[(2-hydroxypropyl)amino]-3-methyl-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

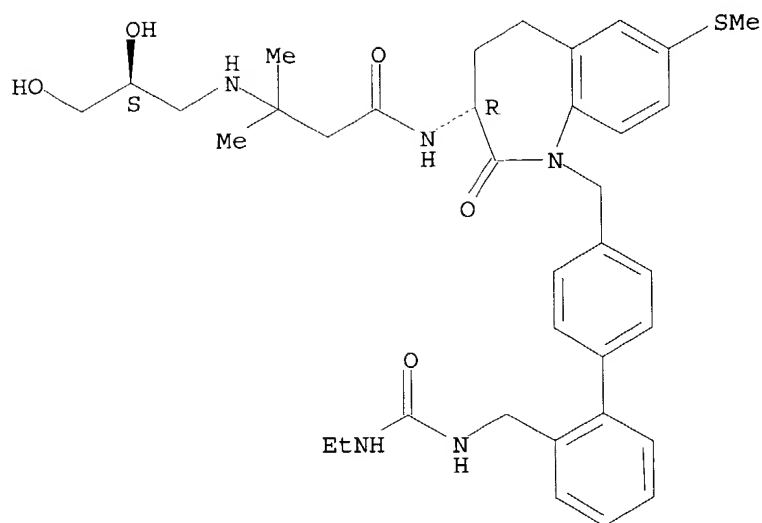
Absolute stereochemistry.



RN 197651-52-8 HCAPLUS

CN Butanamide, 3-[(2,3-dihydroxypropyl)amino]-N-[1-[[2'-[[[(ethylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-3-methyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

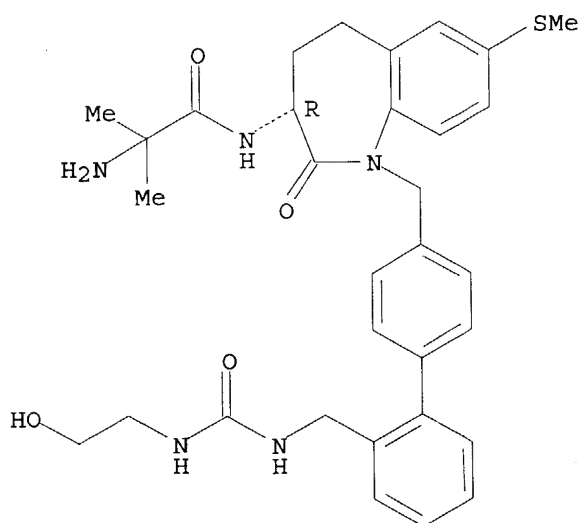
Absolute stereochemistry.



RN 197651-56-2 HCAPLUS

CN Propanamide, 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[(2-hydroxyethyl)amino]carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, (R)- (9CI) (CA INDEX NAME)

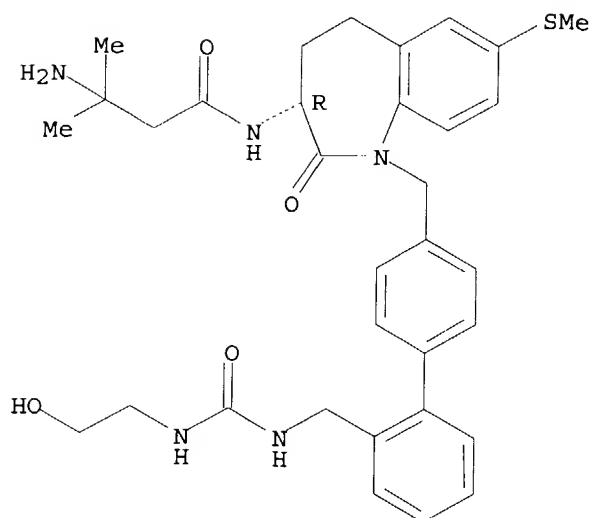
Absolute stereochemistry.



RN 197651-61-9 HCAPLUS

CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[(2-hydroxyethyl)amino]carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, (R)- (9CI) (CA INDEX NAME)

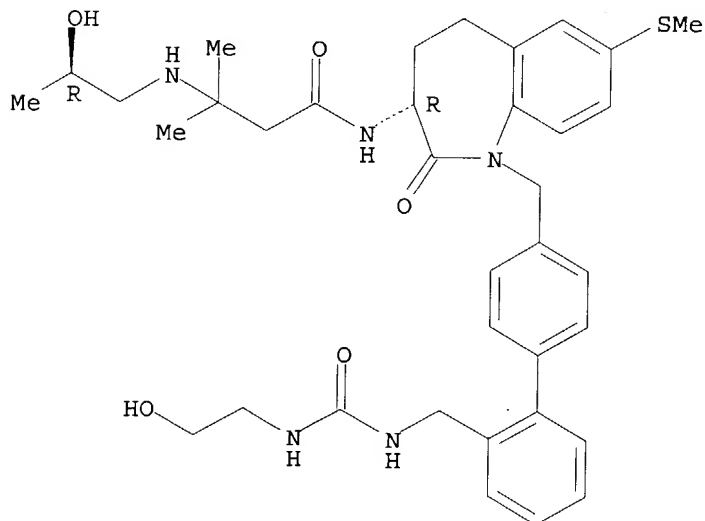
Absolute stereochemistry.



RN 197651-74-4 HCAPLUS

CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[[(2-hydroxyethyl)amino]carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, [R-(R*,R*)]- (9CI)
(CA INDEX NAME)

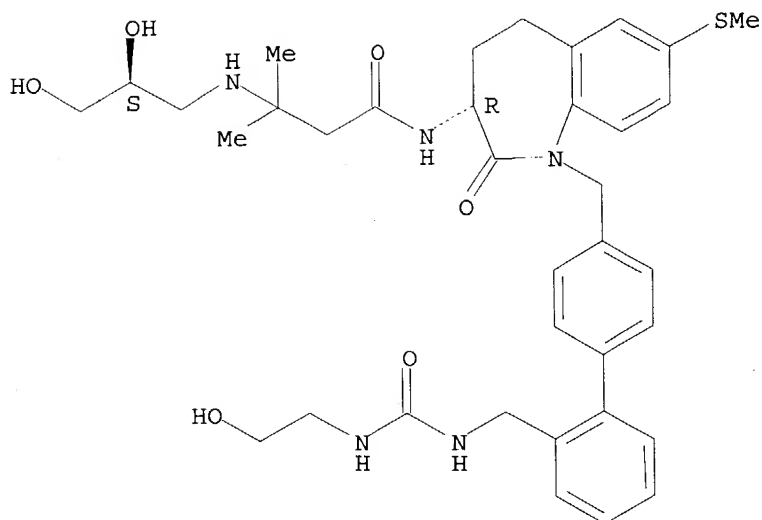
Absolute stereochemistry.



RN 197651-87-9 HCAPLUS

CN Butanamide, 3-[(2,3-dihydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[[(2-hydroxyethyl)amino]carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, [S-(R*,S*)]- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



L52 ANSWER 5 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:902362 HCAPLUS

DOCUMENT NUMBER: 141:379928

ENTRY DATE: Entered STN: 28 Oct 2004

TITLE: Preparation of thiadiazoline derivatives as M-stage kinesin inhibitors

INVENTOR(S): Murakata, Chikara; Yamashita, Yoshinori; Nakai, Ryuichiro; Akasaka, Kazuto; Ino, Yoji; Kato, Kazuhiko; Kitamura, Yuji

PATENT ASSIGNEE(S): Kyowa Hakko Kogyo Co., Ltd., Japan; Fuji Photo Film Co., Ltd.

SOURCE: PCT Int. Appl., 198 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

INT. PATENT CLASSIF.:

MAIN: C07D285-12
SECONDARY: C07D417-04; C07D417-12; A61K031-433; A61K031-4439;
A61K031-5377; A61K031-506; A61P009-04; A61P009-10;
A61P019-02; A61P037-02

CLASSIFICATION: 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1, 63

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004092147	A1	20041028	WO 2004-JP5489	20040416
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,			

ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
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TD, TG

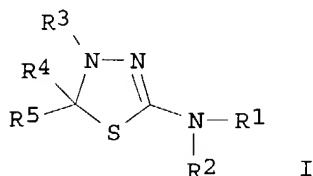
PRIORITY APPLN. INFO.:

JP 2003-114071 A 20030418
JP 2003-164727 A 20030610

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004092147	ICM	C07D285-12
	ICS	C07D417-04; C07D417-12; A61K031-433; A61K031-4439; A61K031-5377; A61K031-506; A61P009-04; A61P009-10; A61P019-02; A61P037-02

GRAPHIC IMAGE:



ABSTRACT:

The title compds. I [R1 represents hydrogen, etc.; R2 represents hydrogen, C(:W)R6 (wherein W represents oxygen or sulfur and R6 represents (un)substituted lower alkyl, etc.), etc.; R3 represents C(:Z)R19 (wherein Z represents oxygen or sulfur and R19 represents (un)substituted lower alkyl, etc.) etc.; R4 represents (un)substituted lower alkyl, etc.; and R5 represents (un)substituted aryl, etc.] are prepared I [R1 = H; R2 = R3 = COCMe3; R4 = (CH2)2NH(CH2)2Me; R5 = phenyl] was prepared in a multistep process starting from thiosemicarbazide hydrochloride and Et benzoylacetate. Compds. of this invention in vitro showed IC50 values of $\leq 2 \mu\text{mol/L}$ against Eg5 ATPase. Formulations are given.

SUPPL. TERM: thiadiazoline deriv prepn M stage kinesin inhibitor
INDEX TERM: Kinesins
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(M stage, Eg5; preparation of thiadiazoline derivs. as M-stage kinesin inhibitors)
INDEX TERM: Human
(preparation of thiadiazoline derivs. as M-stage kinesin inhibitors)
INDEX TERM: 9000-83-3, ATPase
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(Eg5; preparation of thiadiazoline derivs. as M-stage kinesin inhibitors)
INDEX TERM: 781675-01-2P 781675-03-4P 781675-06-7P 781675-10-3P
781675-13-6P 781675-16-9P 781675-17-0P 781675-18-1P
781675-22-7P 781675-25-0P 781675-28-3P 781675-46-5P
781675-50-1P 781675-51-2P 781675-52-3P 781675-63-6P
781675-64-7P 781675-67-0P 781675-68-1P 781675-69-2P
781675-70-5P
ROLE: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of thiadiazoline derivs. as M-stage kinesin inhibitors)

INDEX TERM:

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781675-30-7P	781675-31-8P	781675-32-9P	781675-33-0P
781675-34-1P	781675-35-2P	781675-36-3P	781675-37-4P
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781675-76-1P	781675-77-2P	781675-78-3P	781675-79-4P
781675-80-7P	781675-81-8P		

ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of thiadiazoline derivs. as M-stage kinesin inhibitors)

INDEX TERM:

50-00-0, Formalin, reactions 57-06-7, Allylisothiocyanate
 67-64-1, Acetone, reactions 74-88-4, Methyl iodide,
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 99-91-2, 4'-Chloroacetophenone 99-93-4,
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 110-91-8, Morpholine, reactions 111-42-2, Diethanolamine,
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α -Tetralone 530-93-8, β -Tetralone 540-80-7,
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 585-74-0, 3'-Methylacetophenone 586-37-8,
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 2-Acetylpyrrole 1117-97-1, N,O-Dimethylhydroxylamine
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 1192-62-7, 2-Acetylfuran 1197-09-7, 3',4'-
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 1468-83-3, 3-Acetylthiophene 1501-04-8,
 4-Carbomethoxybutyrophenone 1501-26-4, Methyl
 4-(chloroformyl)butyrate 1579-15-3, 2-Acetoxy-1-indanone
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 3-Chloropropanesulfonyl chloride 1668-10-6, Glycinamide
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 2'-Bromoacetophenone 2550-26-7, Benzylacetone 3144-09-0,
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 3506-36-3, 3-Dimethylaminopropiophenone 3518-65-8,
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 4023-34-1, Cyclopropanecarbonyl chloride 4079-52-1,
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 5468-37-1, 2-Aminoacetophenone hydrochloride 5470-11-1
 5680-79-5 6136-68-1, 3-Acetylbenzonitrile 6610-29-3,
 4-Methylthiosemicarbazide 6638-79-5, N,O-
 Dimethylhydroxylamine hydrochloride 7664-41-7, Ammonia,
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 13431-34-0, 4-Ethylthiosemicarbazide 13679-72-6,
 2-Acetyl-3-methylthiophene 15183-93-4, Thiosemicarbazide
 hydrochloride 16819-79-7 19172-47-5, Lawesson's reagent
 22047-25-2, Acetylpyrazine 22720-75-8 22809-37-6,
 6-Bromohexanoyl chloride 24295-03-2, 2-Acetylthiazole
 24424-99-5, Di-tert-butyl dicarbonate 25333-24-8
 26628-22-8, Sodium azide 26976-88-5 38870-89-2,
 Methoxyacetyl chloride 40635-66-3, 2-Acetoxyisobutyryl
 chloride 42471-59-0, 1-Bromo-3(methoxymethoxy)benzene
 51863-60-6, 3',5'-Dihydroxyacetophenone 57260-73-8,
 tert-Butyl-N-(2-aminoethyl)carbamate 80344-24-7
 89581-82-8 149634-41-3 781675-84-1 781675-85-2
 781675-86-3

ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (preparation of thiadiazoline derivs. as M-stage kinesin
 inhibitors)

INDEX TERM:

108-94-1P, Cyclohexanone, preparation 777-16-2P
 1752-30-3P 2302-93-4P 3115-21-7P 3689-17-6P
 3766-55-0P, 4-Allylthiosemicarbazide 5351-71-3P

5351-80-4P	5424-45-3P	6699-22-5P	6839-90-3P
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ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP
(Preparation); RACT (Reactant or reagent)

(preparation of thiadiazoline derivs. as M-stage kinesin inhibitors)

INDEX TERM: 546112-13-4P 546112-14-5P 546112-15-6P 546112-16-7P
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 546112-29-2P 546112-30-5P 546112-31-6P 546112-32-7P
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 546112-46-3P 546112-47-4P 546112-49-6P 546112-50-9P
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 781675-89-6P 781675-91-0P 781675-92-1P 781675-93-2P
 ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation of thiadiazoline derivs. as M-stage kinesin inhibitors)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD.

REFERENCE(S): (1) Bhalla, M; European Journal of Medicinal Chemistry 1994, V29, P713 HCAPLUS
 (2) Fisons Plc; EP 217519 A1 1987 HCAPLUS
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 (6) Tao, E; US 4338449 A 1982 HCAPLUS

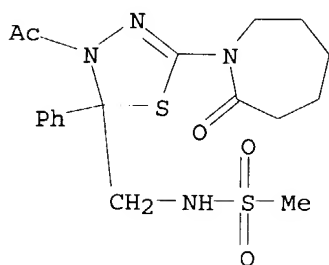
IT 546111-77-7P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of thiadiazoline derivs. as M-stage kinesin inhibitors)

RN 546111-77-7 HCAPLUS

CN 1,3,4-Thiadiazole-2-methanamine, 3-acetyl-5-(hexahydro-2-oxo-1H-azepin-1-yl)-2,3-dihydro-N-(methylsulfonyl)-2-phenyl- (9CI) (CA INDEX NAME)



L52 ANSWER 6 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:696379 HCAPLUS

DOCUMENT NUMBER: 141:225529

ENTRY DATE: Entered STN: 26 Aug 2004

TITLE: Preparation of hexahydropyrazino[1,2-a]pyrimidine-4,7-diones as anorectic agents.

INVENTOR(S): Flohr, Stefanie; Stengelin, Siegfried; Gossel, Matthias; Klabunde, Thomas; Stahl, Petra; Safar, Pavel; Spoonamore, James; Smrcina, Martin; Klein,

PATENT ASSIGNEE(S): Joseph T.; Merriman, Gregory H.; Whiteley, Brian K.;
 SOURCE: Lanter, Carolina; Bordeau, Kenneth J.; Yang, Zhaoxia
 Aventis Pharma Deutschland GmbH, Germany
 PCT Int. Appl., 270 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 INT. PATENT CLASSIF.:
 MAIN: C07D487-04
 SECONDARY: A61K031-519; A61P003-04; C07D241-00; C07D239-00
 CLASSIFICATION: 28-16 (Heterocyclic Compounds (More Than One Hetero
 Atom))
 Section cross-reference(s): 1, 34
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004072077	A1	20040826	WO 2004-EP770	20040129
W:	AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI			
RW:	BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
DE 10305885	A1	20040826	DE 2003-10305885	20030213
PRIORITY APPLN. INFO.:			DE 2003-10305885	A 20030213
			DE 2003-10349671	A 20031024

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004072077	ICM	C07D487-04
	ICS	A61K031-519; A61P003-04; C07D241-00; C07D239-00
OTHER SOURCE(S):		MARPAT 141:225529
GRAPHIC IMAGE:		

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

ABSTRACT:

Title compds. I [Z = (CH₂)_m-A; A = 3-12 membered mono, bi, or spirobicyclic ring; m = 0-6; Y = (CH₂)_n; n = 0-1; R₁ = alkanyl, alkenyl, alkynyl, etc.; R₂ = H, halo, OH, etc.; R₃, R₄, R₅ = H, halo, OH, etc.] and their pharmaceutically acceptable salts were prepared. For example, sodium cyanoborohydride mediated reductive amination of amine II, e.g., prepared via the sequential peptide coupling of isopropylamine, Fmoc-(S)-4-chlorophenylalanine, Z-Dap(Fmoc) and 2-methoxy-5-chlorobenzenesulfonyl chloride on bromoacetal-linker resin, followed by formic acid cleavage-condensation-cyclization, with acetaldehyde afforded pyrazinopyrimidine III. Compds. I are claimed useful for the treatment of anorexia.

SUPPL. TERM: hexahydropyrazinopyrimidinyldione prepn solid phase

synthesis; antianorexia agent hexahydropyrazinopyrimidinyl di
 one prepn
 INDEX TERM: Drugs
 (appetite stimulants, medicaments with; preparation of
 pyrazinopyrimidinylidiones as anorectic agents.)
 INDEX TERM: Sexual behavior
 (disorder, treatment of; preparation of
 pyrazinopyrimidinylidiones as anorectic agents.)
 INDEX TERM: Combination chemotherapy
 (medicaments with; preparation of pyrazinopyrimidinylidiones as
 anorectic agents.)
 INDEX TERM: Disease, animal
 (metabolic syndrome X, treatment of; preparation of
 pyrazinopyrimidinylidiones as anorectic agents.)
 INDEX TERM: Diabetes mellitus
 (non-insulin-dependent, treatment of; preparation of
 pyrazinopyrimidinylidiones as anorectic agents.)
 INDEX TERM: Human
 Solid phase synthesis
 (preparation of pyrazinopyrimidinylidiones as anorectic
 agents.)
 INDEX TERM: Appetite
 (stimulants, medicaments with; preparation of
 pyrazinopyrimidinylidiones as anorectic agents.)
 INDEX TERM: Anorexia
 Antidiabetic agents
 Antiobesity agents
 Cachexia
 Obesity
 (treatment of; preparation of pyrazinopyrimidinylidiones as
 anorectic agents.)
 INDEX TERM: 9028-35-7
 ROLE: BSU (Biological study, unclassified); BIOL (Biological
 study)
 (medicaments with; preparation of pyrazinopyrimidinylidiones as
 anorectic agents.)
 INDEX TERM: 746671-85-2P 746671-87-4P 746672-05-9P 748160-40-9P
 ROLE: PAC (Pharmacological activity); RCT (Reactant); SPN
 (Synthetic preparation); THU (Therapeutic use); BIOL
 (Biological study); PREP (Preparation); RACT (Reactant or
 reagent); USES (Uses)
 (preparation of pyrazinopyrimidinylidiones as anorectic
 agents.)
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 748160-65-8P **748160-66-9P** 748160-67-0P

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748162-34-7P	748162-35-8P	748162-36-9P	748162-37-0P

ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of pyrazinopyrimidinylidiones as anorectic agents.)

INDEX TERM:

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748162-42-7P	748162-43-8P	748162-44-9P	748162-45-0P
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ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of pyrazinopyrimidinyldiones as anorectic agents.)

INDEX TERM:

50-00-0, Formaldehyde, reactions 55-86-7 67-64-1,
Acetone, reactions 75-07-0, Acetaldehyde, reactions
75-31-0, Isopropylamine, reactions 76-05-1, reactions
78-84-2, Isobutyraldehyde 98-09-9, Benzenesulfonyl
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Allylamine 108-24-7, Acetic acid anhydride 108-94-1,
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109-90-0, Ethylisocyanate 110-52-1, 1,4-Dibromobutane
110-91-8, Morpholine, reactions 111-24-0,
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376595-03-8 678991-30-5 678991-65-6 746672-87-7
746672-88-8 748162-98-3 748163-22-6 748163-99-7
748164-00-3

ROLE: RCT (Reactant); RACT (Reactant or reagent)

(preparation of pyrazinopyrimidinyldiones as anorectic agents.)

INDEX TERM:

122-01-0P, 4-Chlorobenzoyl chloride 80179-37-9P

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ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of pyrazinopyrimidinyldiones as anorectic agents.)

IT 748160-66-9P

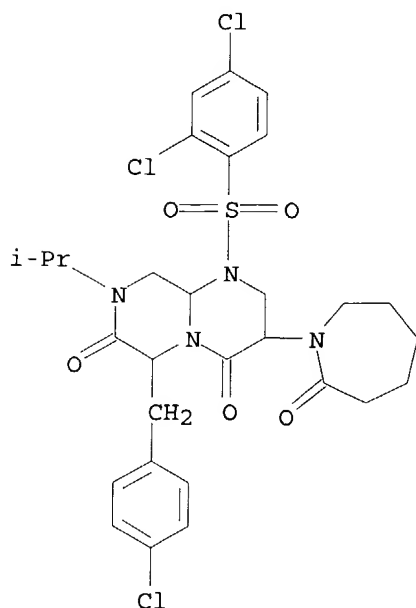
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

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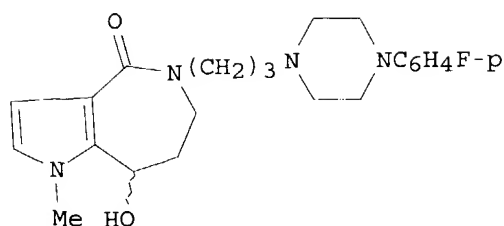
RN 748160-66-9 HCAPLUS

CN 2H-Pyrazino[1,2-a]pyrimidine-4,7(3H,6H)-dione, 6-[(4-chlorophenyl)methyl]-

1-[(2,4-dichlorophenyl)sulfonyl]-3-(hexahydro-2-oxo-1H-azepin-1-yl)tetrahydro-8-(1-methylethyl)- (9CI) (CA INDEX NAME)



L52 ANSWER 7 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2000:311250 HCAPLUS
 DOCUMENT NUMBER: 133:104983
 ENTRY DATE: Entered STN: 14 May 2000
 TITLE: Synthesis and serotonin 2 (5-HT₂) receptor antagonist activity of 5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and related compounds
 AUTHOR(S): Mizuno, Akira; Ogata, Atsuto; Kamei, Tomoe; Shibata, Makoto; Shimamoto, Tetsuo; Hayashi, Yasuhiro; Nakanishi, Kyoko; Takiguchi, Chikako; Oka, Naomi; Inomata, Norio
 CORPORATE SOURCE: Suntory Institute for Biomedical Research, Osaka, 618-8503, Japan
 SOURCE: Chemical & Pharmaceutical Bulletin (2000), 48(5), 623-635
 CODEN: CPBTAL; ISSN: 0009-2363
 PUBLISHER: Pharmaceutical Society of Japan
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 CLASSIFICATION: 28-2 (Heterocyclic Compounds (More Than One Hetero Atom))
 Section cross-reference(s): 1
 OTHER SOURCE(S): CASREACT 133:104983
 GRAPHIC IMAGE:



I

ABSTRACT:

A series of 5-aminoalkylpyrrolo[3,2-c]azepine derivs. was synthesized and their serotonin 2 (5-HT₂) receptor antagonist and antiplatelet aggregation activities were evaluated. 5-HT₂ receptor antagonist activity was largely determined by the nature of the substituent at the 8-position as well as the aminoalkyl group at the 5-position of the pyrrolo[3,2-c]azepine ring. Compound I was recognized as having potent 5-HT₂ receptor antagonist activity with weak α_1 adrenoceptor blocking activity and no significant D₂ receptor binding affinity. (\pm)-I was resolved directly via diastereomeric salt formation and each enantiomer was evaluated. The 5-HT₂ receptor antagonist activity of I was found to reside primarily in (-)-I (α -OH) (which was about 14-fold more potent than (+)-I (β -OH) in isolated guinea pig arteries). Consequently, (S)-(-)-I (SUN C5174) displayed the overall best profile with potent 5-HT₂ receptor antagonist activity ($pA_2=8.98\pm0.06$) and high selectivity vs. other receptors. SUN C5174 showed a marked inhibitory effect on the platelet aggregation induced by serotonin in combination with collagen and ADP in canine or human platelet-rich plasma ($IC_{50}=6.5$ to 16 nM). SUN C5174 significantly inhibited the mortality rate in mouse acute pulmonary thromboembolic death induced by collagen and serotonin at oral doses of 0.3 mg/kg or higher. SUN C5174 is currently undergoing clin. evaluation.

SUPPL. TERM: pyrroloazepine prepn serotonin 5HT₂ receptor antagonist;
serotonin induced platelet aggregation inhibition
pyrroloazepine SUN C5174

INDEX TERM: 5-HT antagonists
(5-HT_{2A}; preparation and serotonin 2 (5-HT₂) receptor
antagonist activity of 5-aminoalkyl-substituted
pyrrolo[3,2-c]azepines and related compds.)

INDEX TERM: Crystal structure
Molecular structure
(of fluorophenylpiperazinypropyl pyrrolo[3,2-
c]azepinoone derivative)

INDEX TERM: Structure-activity relationship
(platelet aggregation-inhibiting; preparation and serotonin 2
(5-HT₂) receptor antagonist activity of
5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and
related compds.)

INDEX TERM: Heterocyclization
Platelet aggregation inhibitors
(preparation and serotonin 2 (5-HT₂) receptor antagonist
activity of 5-aminoalkyl-substituted pyrrolo[3,2-
c]azepines and related compds.)

INDEX TERM: Structure-activity relationship
(receptor-inhibiting; preparation and serotonin 2 (5-HT₂)
receptor antagonist activity of 5-aminoalkyl-substituted
pyrrolo[3,2-c]azepines and related compds.)

INDEX TERM: 282550-44-1P
ROLE: PRP (Properties); SPN (Synthetic preparation); PREP

(Preparation)
(crystal structure; preparation and serotonin 2 (5-HT₂)
receptor antagonist activity of 5-aminoalkyl-substituted
pyrrolo[3,2-c]azepines and related compds.)

INDEX TERM: 191592-02-6P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP
(Preparation); RACT (Reactant or reagent)
(nod *preparation and serotonin 2 (5-HT₂) receptor antagonist
activity of 5-aminoalkyl-substituted pyrrolo[3,2-
c]azepines and related compds.)

INDEX TERM: 74050-98-9, Ketanserin 125926-17-2, Sarpogrelate
135963-42-7
ROLE: BAC (Biological activity or effector, except adverse);
BSU (Biological study, unclassified); BIOL (Biological
study)
(preparation and serotonin 2 (5-HT₂) receptor antagonist
activity of 5-aminoalkyl-substituted pyrrolo[3,2-
c]azepines and related compds.)

INDEX TERM: 191591-86-3P 191591-92-1P 191592-08-2P 191592-09-3P
191592-10-6P 191592-12-8P 191592-13-9P 191592-14-0P
191592-16-2P 191592-17-3P 191592-18-4P 191592-19-5P
191592-20-8P 191592-21-9P 191592-22-0P 191592-23-1P
191592-24-2P 191592-25-3P 191592-27-5P 191592-30-0P
282550-43-0P
ROLE: BAC (Biological activity or effector, except adverse);
BSU (Biological study, unclassified); RCT (Reactant); SPN
(Synthetic preparation); BIOL (Biological study); PREP
(Preparation); RACT (Reactant or reagent)
(preparation and serotonin 2 (5-HT₂) receptor antagonist
activity of 5-aminoalkyl-substituted pyrrolo[3,2-
c]azepines and related compds.)

INDEX TERM: 191592-15-1P 191592-35-5P 191592-36-6P
282550-35-0P 282550-39-4P
ROLE: BAC (Biological activity or effector, except adverse);
BSU (Biological study, unclassified); SPN (Synthetic
preparation); BIOL (Biological study); PREP (Preparation)
(preparation and serotonin 2 (5-HT₂) receptor antagonist
activity of 5-aminoalkyl-substituted pyrrolo[3,2-
c]azepines and related compds.)

INDEX TERM: 282550-33-8P
ROLE: BYP (Byproduct); PREP (Preparation)
(preparation and serotonin 2 (5-HT₂) receptor antagonist
activity of 5-aminoalkyl-substituted pyrrolo[3,2-
c]azepines and related compds.)

INDEX TERM: 75-03-6, Iodoethane 87-69-4, L-(+)-Tartaric acid,
reactions 109-70-6, 1-Bromo-3-chloropropane 140-88-5,
Ethyl acrylate 147-71-7, D-(-)-Tartaric acid 931-03-3,
1H-Pyrrole-3-carboxylic acid 2252-63-3,
1-(4-Fluorophenyl)piperazine 2703-17-5, Methyl
pyrrole-3-carboxylate 6276-54-6, 3-Chloropropylamine
hydrochloride 25519-78-2, 4-(4-Fluorobenzoyl)piperidine
hydrochloride 27019-47-2, β -Alanine benzyl ester
p-toluenesulfonate 99972-42-6
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation and serotonin 2 (5-HT₂) receptor antagonist
activity of 5-aminoalkyl-substituted pyrrolo[3,2-
c]azepines and related compds.)

INDEX TERM: 36929-61-0P 40611-74-3P, Methyl 1-methyl-1H-pyrrole-3-
carboxylate 155177-46-1P 191591-53-4P 191591-55-6P
191591-57-8P 191591-59-0P 191591-61-4P 191591-63-6P

191591-64-7P 191591-68-1P 191591-69-2P 191591-70-5P
 191591-71-6P 191591-72-7P 191591-74-9P 191591-75-0P
 191591-77-2P 191591-80-7P 191591-81-8P 191591-82-9P
 191591-85-2P 191591-87-4P 191591-89-6P 191591-90-9P
 191591-91-0P 191591-93-2P 191591-94-3P 191591-95-4P
 191591-96-5P 191591-97-6P 191591-98-7P 191591-99-8P
 191592-00-4P 191592-01-5P **191592-05-9P**
 191592-38-8P 282550-40-7P 282550-41-8P 282550-42-9P

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and serotonin 2 (5-HT₂) receptor antagonist activity of 5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and related compds.)

INDEX TERM:

191591-62-5P 191591-65-8P 282550-34-9P

ROLE: SPN (Synthetic preparation); PREP (Preparation)
 (preparation and serotonin 2 (5-HT₂) receptor antagonist activity of 5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and related compds.)

REFERENCE COUNT:

49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD.

REFERENCE(S) :

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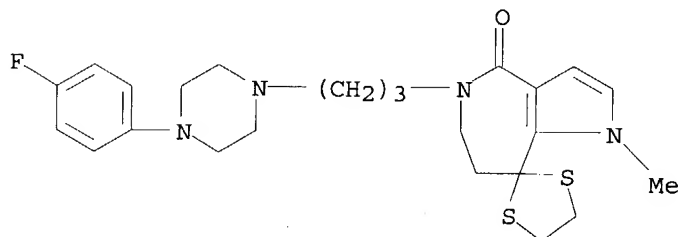
IT 282550-35-0P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(preparation and serotonin 2 (5-HT₂) receptor antagonist activity of 5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and related compds.)

RN 282550-35-0 HCAPLUS

CN Spiro[1,3-dithiolane-2,8'-(1'H)-pyrrolo[3,2-c]azepin]-4'-(5'H)-one, 5'-[3-[4-(4-fluorophenyl)-1-piperazinyl]propyl]-6',7'-dihydro-1'-methyl-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

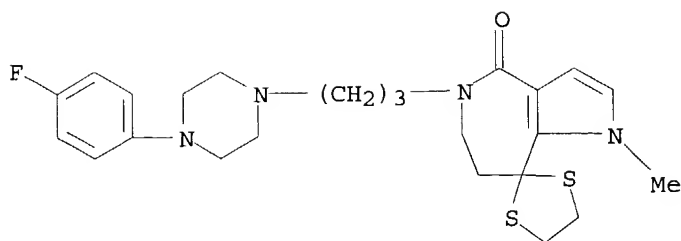
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RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

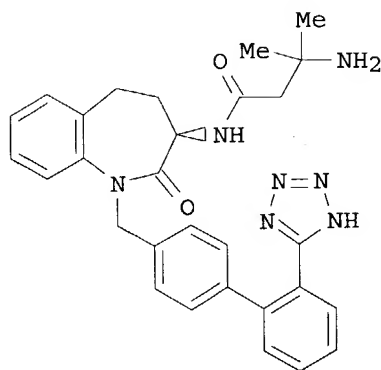
(preparation and serotonin 2 (5-HT₂) receptor antagonist activity of 5-aminoalkyl-substituted pyrrolo[3,2-c]azepines and related compds.)

RN 191592-05-9 HCAPLUS

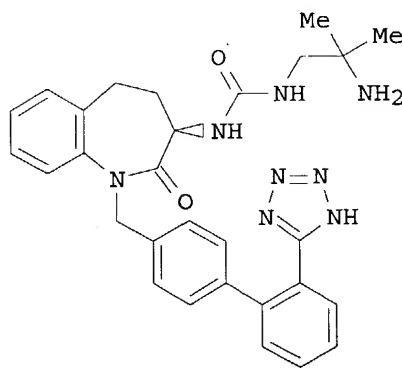
CN Spiro[1,3-dithiolane-2,8'-(1'H)-pyrrolo[3,2-c]azepin]-4'-(5'H)-one, 5'-[3-[4-(4-fluorophenyl)-1-piperazinyl]propyl]-6',7'-dihydro-1'-methyl-, dihydrochloride (9CI) (CA INDEX NAME)



L52 ANSWER 8 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1997:49724 HCAPLUS
 DOCUMENT NUMBER: 126:171471
 ENTRY DATE: Entered STN: 23 Jan 1997
 TITLE: Benzolactam growth hormone secretagogues: replacement of the C-3 amide bond in L-692,429
 AUTHOR(S): Ok, Hyun O.; Szumiloski, John L.; Doldouras, George A.; Schoen, William R.; Cheng, Kang; Chan, Wanda W.-S.; Butler, Bridget S.; Smith, Roy G.; Fisher, Michael H.; Wyvratt, Matthew J.
 CORPORATE SOURCE: Departments Medicinal Chemistry Biochemistry Physiology, Merck Research Laboratories, Rahway, NJ, 07065, USA
 SOURCE: Bioorganic & Medicinal Chemistry Letters (1996), 6(24), 3051-3056
 CODEN: BMCLE8; ISSN: 0960-894X
 PUBLISHER: Elsevier
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 CLASSIFICATION: 27-21 (Heterocyclic Compounds (One Hetero Atom))
 Section cross-reference(s): 1, 25
 GRAPHIC IMAGE:



I



II

ABSTRACT:

The synthesis and structure-activity relationships of various C-3 amide bond modifications in the novel non-peptidyl growth hormone secretagogue L-692,429 (I) were described. An example derivative was II. Several C-3 amide surrogates were prepared and the urea moiety was found to exhibit growth hormone releasing activity similar to that observed with L-692,429.

SUPPL. TERM: growth hormone L 692429 deriv prepn; structure activity
growth hormone L 692429; benzolactam prepn growth hormone L
692429

INDEX TERM: Structure-activity relationship
(preparation of L-692429 analogs as growth hormone
secretagogues)

INDEX TERM: 145455-23-8DP, L-692429, analogs
ROLE: BAC (Biological activity or effector, except adverse);
BSU (Biological study, unclassified); SPN (Synthetic
preparation); BIOL (Biological study); PREP (Preparation)
(Benzolactam growth hormone secretagogues: replacement of
the C-3 amide bond in L-692,429)

INDEX TERM: 9034-39-3, Growth hormone releasing factor 145456-63-9
187107-71-7
ROLE: BAC (Biological activity or effector, except adverse);
BSU (Biological study, unclassified); BIOL (Biological
study)
(preparation of L-692429 analogs as growth hormone
secretagogues)

INDEX TERM: 140700-64-7P 145455-29-4P 145455-36-3P 145456-61-7P
156197-47-6P 169953-04-2P 169953-34-8P 169954-56-7P
187107-70-6P **187107-72-8P 187107-73-9P**
187107-74-0P 187107-75-1P
ROLE: BAC (Biological activity or effector, except adverse);
BSU (Biological study, unclassified); SPN (Synthetic
preparation); BIOL (Biological study); PREP (Preparation)
(preparation of L-692429 analogs as growth hormone
secretagogues)

INDEX TERM: 124-68-5 42514-50-1 81445-44-5 81445-45-6
124750-51-2 137036-55-6 169954-70-5 187107-78-4
187107-79-5 187107-80-8 187107-81-9
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation of L-692429 analogs as growth hormone
secretagogues)

INDEX TERM: 109608-77-7P 145485-84-3P 145485-87-6P 181646-38-8P
187107-76-2P 187107-77-3P 187107-82-0P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP
(Preparation); RACT (Reactant or reagent)
(preparation of L-692429 analogs as growth hormone
secretagogues)

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS
RECORD.

REFERENCE(S): (1) Armstrong, J; Tetrahedron Lett 1994, V35, P3239 HCAPLUS
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HCAPLUS
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HCAPLUS
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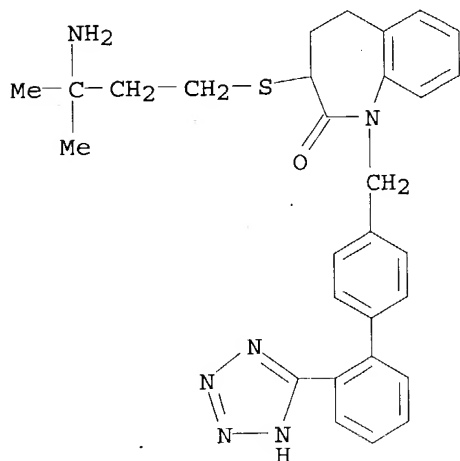
IT **187107-72-8P 187107-73-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); SPN (Synthetic preparation); BIOL (Biological

study); PREP (Preparation)

(preparation of L-692429 analogs as growth hormone secretagogues)

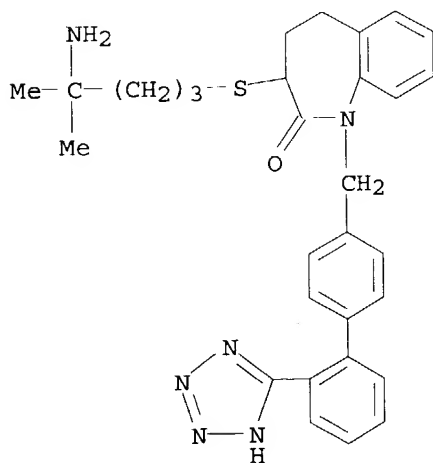
RN 187107-72-8 HCAPLUS

CN 2H-1-Benzazepin-2-one, 3-[(3-amino-3-methylbutyl)thio]-1,3,4,5-tetrahydro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



RN 187107-73-9 HCAPLUS

CN 2H-1-Benzazepin-2-one, 3-[(4-amino-4-methylpentyl)thio]-1,3,4,5-tetrahydro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L52 ANSWER 9 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:902676 HCAPLUS

DOCUMENT NUMBER: 123:313795

ENTRY DATE: Entered STN: 08 Nov 1995

TITLE: Preparation of ureidobenzaepinones as growth hormone

release stimulants

INVENTOR(S): Ok, Hyun O.; Schoen, William R.; Szumiloski, John

PATENT ASSIGNEE(S): Merck and Co., Inc., USA

SOURCE: PCT Int. Appl., 145 pp.

DOCUMENT TYPE: CODEN: PIXXD2
 LANGUAGE: Patent
 English
 INT. PATENT CLASSIF.:
 MAIN: C07D223-16
 SECONDARY: C07D261-10; A61K031-55
 CLASSIFICATION: 27-21 (Heterocyclic Compounds (One Hetero Atom))
 Section cross-reference(s): 1
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

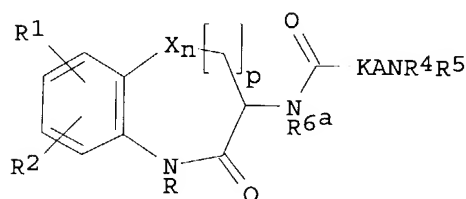
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9516675	A1	19950622	WO 1994-US14374	19941209
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9513718	A1	19950703	AU 1995-13718	19941209
PRIORITY APPLN. INFO.:			US 1993-149482	19931213
			WO 1994-US14374	19941209

PATENT CLASSIFICATION CODES:

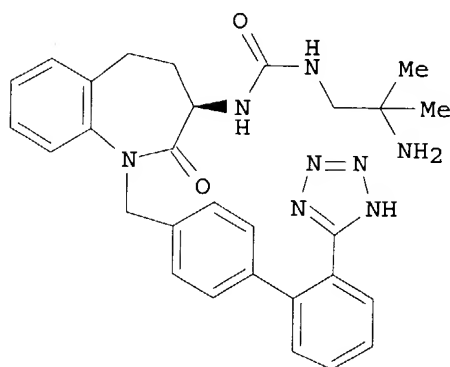
PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9516675	ICM	C07D223-16
	ICS	C07D261-10; A61K031-55
		MARPAT 123:313795

OTHER SOURCE(S):

GRAPHIC IMAGE:



I



II

ABSTRACT:

Title compds. [I; A = (1h)xCR8aR8b(CH2)y; K = O, S, NR6b; R = (CH2)qLwR3; L = (un)substituted phenylene; R1,R2 = H, halo, (perfluoro)alkyl, etc.; R3 =

(un)substituted Ph; R4,R5,R8a,R8b = H, alkyl, (un)substituted Ph, etc.; NR4R5 = heterocyclyl; R6a,R6b = H, (phenyl)alkyl, Ph, etc.; X = CO, O, SOO-2, CH(OH), NH, CH:CH, etc.; n,w = 0 or 1; p,x,y, = 0-3; q = 0-4] were prepared as growth hormone release stimulants (no data). Thus, H2NCH2CMe2NHCO2CMe3 (preparation given) was treated with COCl2 and the product condensed with 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one to give the urea which was N-alkylated with N-triphenylmethyl-5-(4'-bromomethyl-2-biphenyl)tetrazole to give, after deprotection, title compound II.

SUPPL. TERM: ureidobenzaepinone prepn growth hormone release stimulant
INDEX TERM: 169953-04-2P 169953-05-3P **169953-06-4P**

169953-07-5P	169953-08-6P	169953-09-7P	169953-10-0P
169953-11-1P	169953-12-2P	169953-13-3P	
169953-14-4P	169953-15-5P	169953-16-6P	169953-17-7P
169953-18-8P	169953-19-9P	169953-20-2P	
169953-21-3P	169953-22-4P	169953-23-5P	169953-24-6P
169953-25-7P	169953-26-8P	169953-27-9P	
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ROLE: BAC (Biological activity or effector, except adverse);
BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of ureidobenzaepinones as growth hormone release stimulants)

INDEX TERM: 9002-72-6, Growth hormone
 ROLE: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (preparation of ureidobenzaepinones as growth hormone release stimulants)

INDEX TERM: 110-87-2 501-53-1, Benzyl chloroformate 577-19-5, 2-Bromonitrobenzene 811-93-8, 1,2-Diamino-2-methylpropane 5720-05-8, 4-Tolylboronic acid 7699-00-5, Ethyl D-lactate 24424-99-5, Di-tert-butyl dicarbonate 30674-80-7 81445-44-5, (S)-2-Benzyloxypropanal 124750-51-2 169954-84-1
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (preparation of ureidobenzaepinones as growth hormone release stimulants)

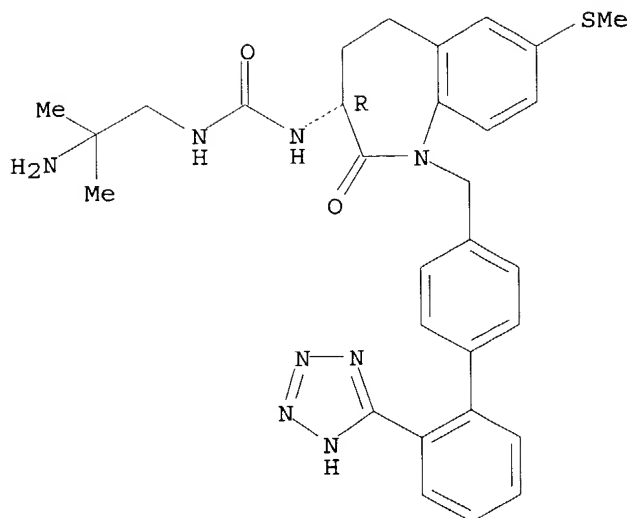
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 ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation of ureidobenzaepinones as growth hormone release stimulants)

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 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (preparation of ureidobenzaepinones as growth hormone release stimulants)

RN 169953-06-4 HCAPLUS

CN Urea, N-(2-amino-2-methylpropyl)-N'-[2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, (R)- (9CI) (CA INDEX NAME)

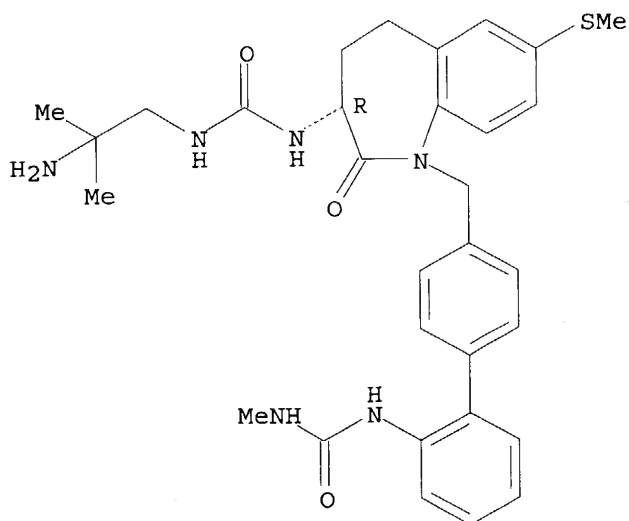
Absolute stereochemistry.



RN 169953-11-1 HCAPLUS

CN Urea, N-[4'-[[3-[[[(2-amino-2-methylpropyl)amino]carbonyl]amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-yl]-N'-methyl-, (R)- (9CI) (CA INDEX NAME)

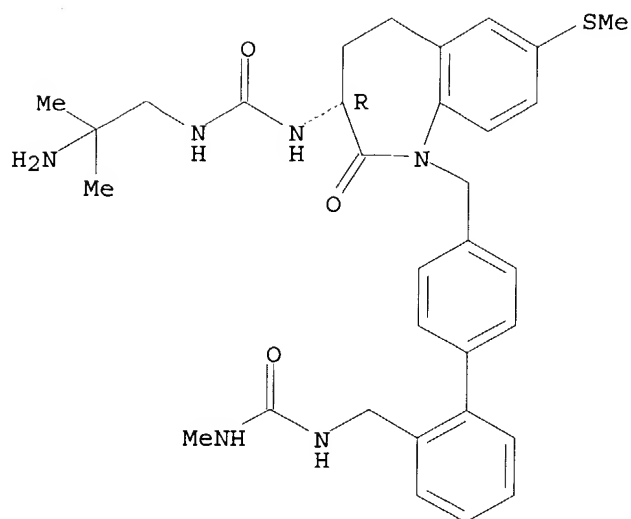
Absolute stereochemistry.



RN 169953-18-8 HCAPLUS

CN Urea, N-[[4'-[[3-[[[(2-amino-2-methylpropyl)amino]carbonyl]amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-yl]methyl]-N'-methyl-, (R)- (9CI) (CA INDEX NAME)

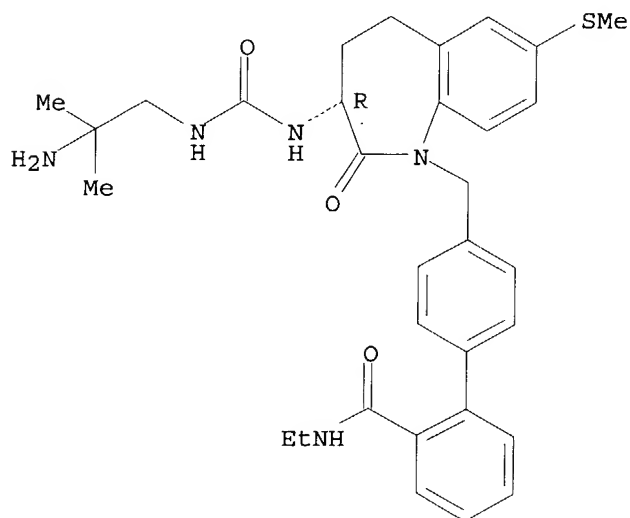
Absolute stereochemistry.



RN 169953-20-2 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxamide, 4'-[[3-[[[(2-amino-2-methylpropyl)amino]carbonyl]amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl]-N-ethyl-, (R)- (9CI) (CA INDEX NAME)

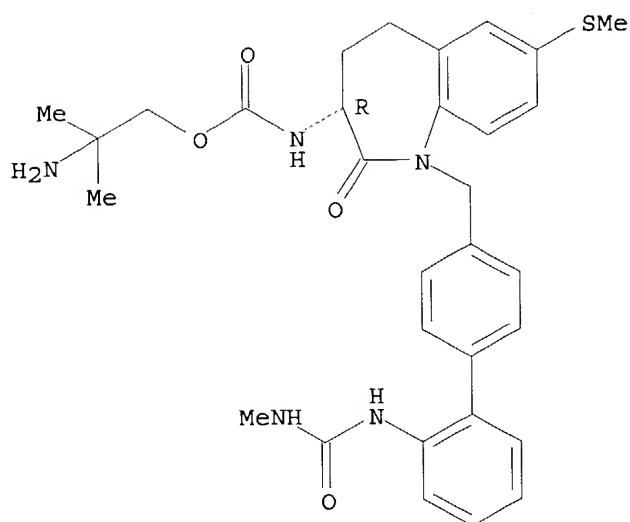
Absolute stereochemistry.



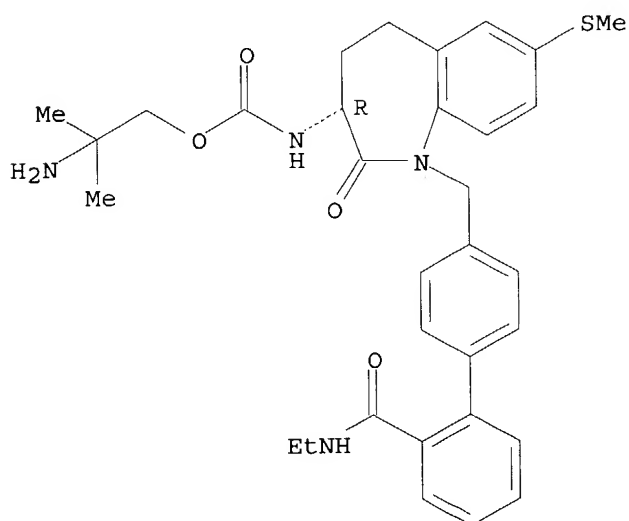
RN 169953-25-7 HCAPLUS

CN Carbamic acid, [2,3,4,5-tetrahydro-1-[[2'-[[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]]-, 2-amino-2-methylpropyl ester, (R)- (9CI) (CA INDEX NAME)

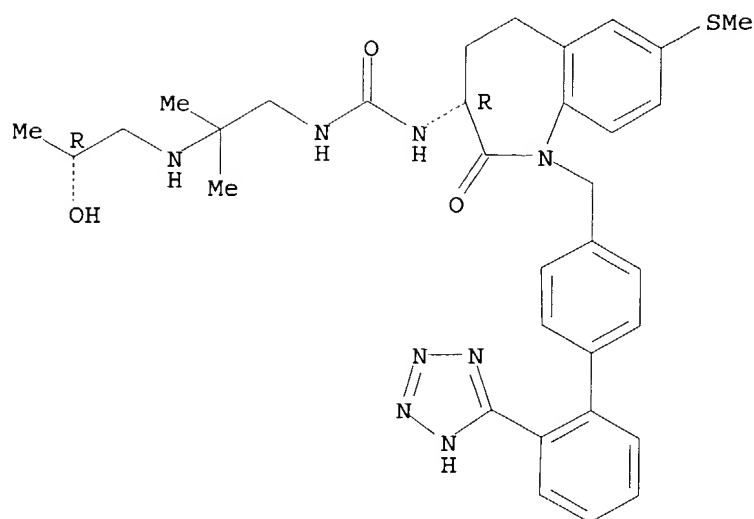
Absolute stereochemistry.



Absolute stereochemistry.

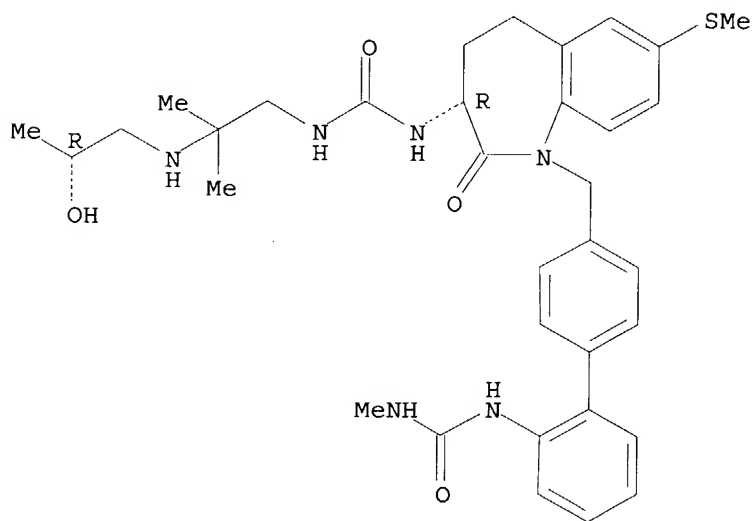


Absolute stereochemistry.



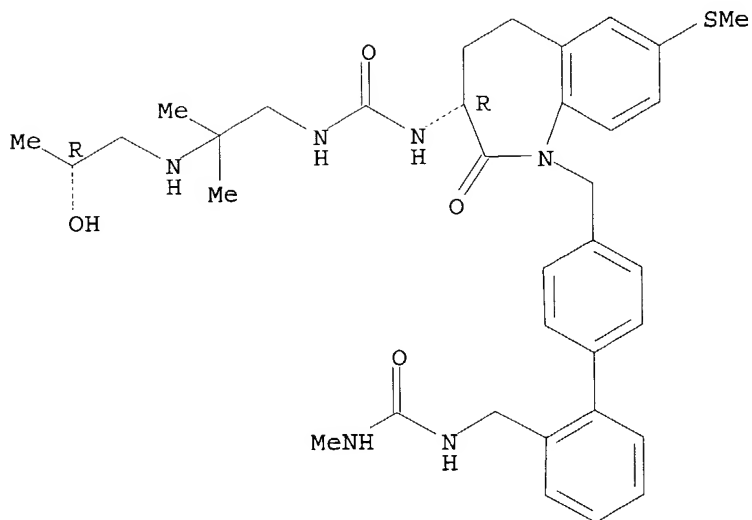
RN 169953-41-7 HCAPLUS
 CN Urea, N-[2-[(2-hydroxypropyl)amino]-2-methylpropyl]-N'-[2,3,4,5-tetrahydro-1-[[2'-[[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, [R-(R*,R*)]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 169953-48-4 HCAPLUS
 CN Urea, N-[2-[(2-hydroxypropyl)amino]-2-methylpropyl]-N'-[2,3,4,5-tetrahydro-1-[[2'-[[[(methylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, [R-(R*,R*)]]- (9CI) (CA INDEX NAME)

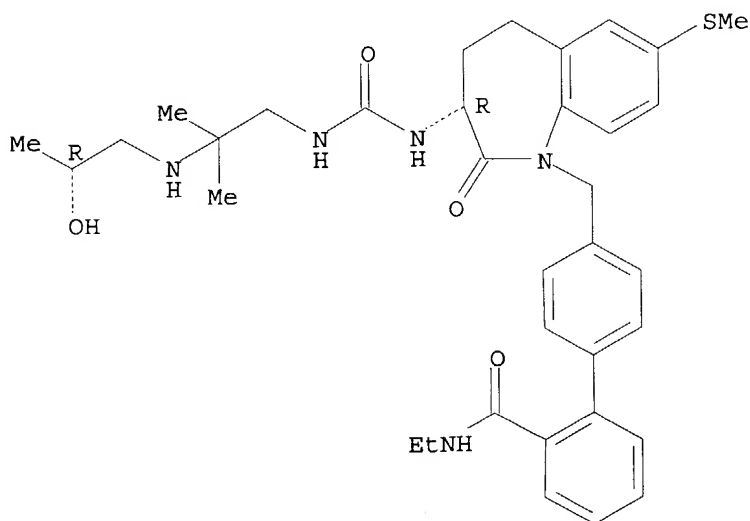
Absolute stereochemistry.



RN 169953-50-8 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxamide, N-ethyl-4'-[[2,3,4,5-tetrahydro-3-[[[2-[(2-hydroxypropyl)amino]-2-methylpropyl]amino]carbonyl]amino]-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

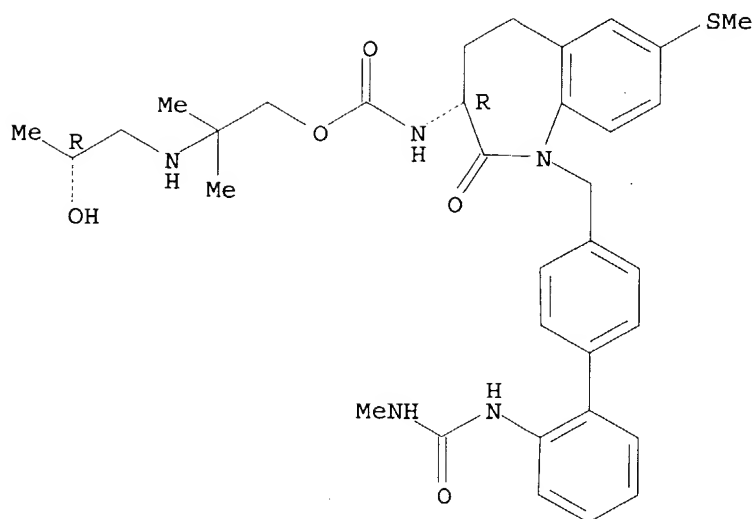
Absolute stereochemistry.



RN 169953-55-3 HCAPLUS

CN Carbamic acid, [2,3,4,5-tetrahydro-1-[[2'-[[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, 2-[(2-hydroxypropyl)amino]-2-methylpropyl ester, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

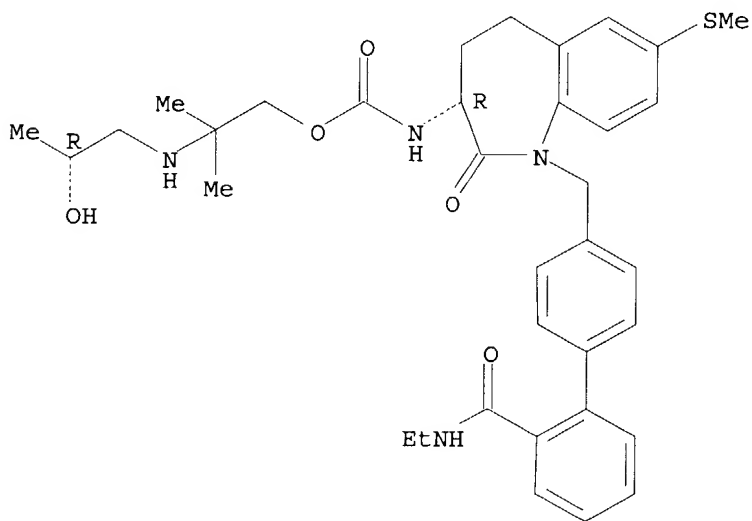
Absolute stereochemistry.



RN 169953-63-3 HCAPLUS

CN Carbamic acid, [1-[[2'-[(ethylamino)carbonyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, 2-[(2-hydroxypropyl)amino]-2-methylpropyl ester, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

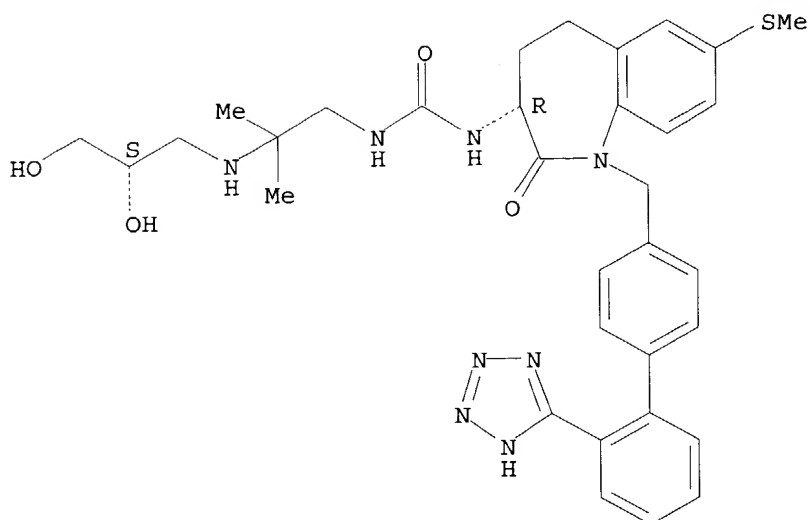
Absolute stereochemistry.



RN 169953-66-6 HCAPLUS

CN Urea, N-[2-[(2,3-dihydroxypropyl)amino]-2-methylpropyl]-N'-[2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

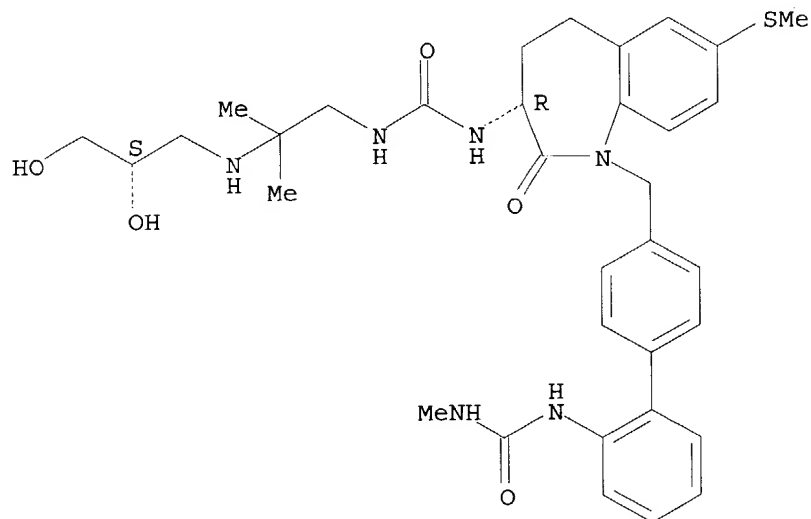
Absolute stereochemistry.



RN 169953-71-3 HCAPLUS

CN Urea, N-[4'-[[3-[[[2-[(2,3-dihydroxypropyl)amino]-2-methylpropyl]amino]carbonyl]amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-yl]-N'-methyl-, [S-(R*,S*)]-(9CI) (CA INDEX NAME)

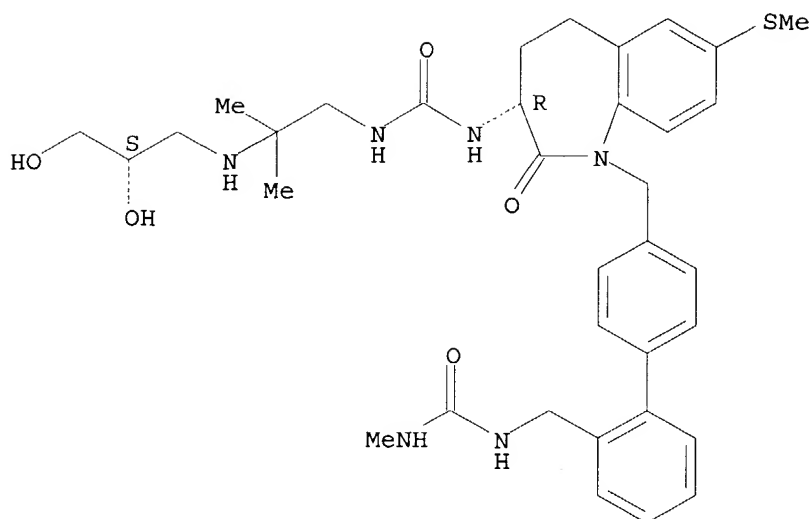
Absolute stereochemistry.



RN 169953-78-0 HCAPLUS

CN Urea, N-[[4'-[[3-[[[2-[(2,3-dihydroxypropyl)amino]-2-methylpropyl]amino]carbonyl]amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-yl]methyl]-N'-methyl-, [S-(R*,S*)]-(9CI) (CA INDEX NAME)

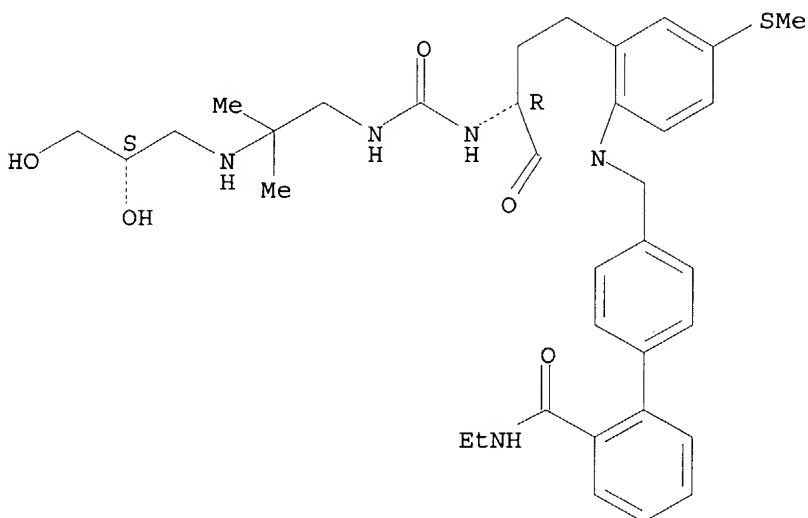
Absolute stereochemistry.



RN 169953-80-4 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxamide, 4'-[[[3-[[[2-[(2,3-dihydroxypropyl)amino]-2-methylpropyl]amino]carbonyl]amino]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-1-yl]methyl]-N-ethyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

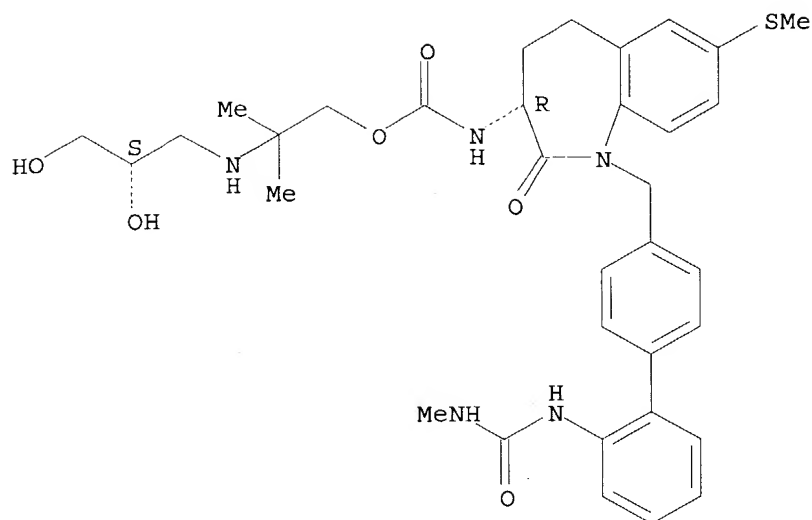
Absolute stereochemistry.



RN 169953-85-9 HCAPLUS

CN Carbamic acid, [2,3,4,5-tetrahydro-1-[[2'-[[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, 2-[(2,3-dihydroxypropyl)amino]-2-methylpropyl ester, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

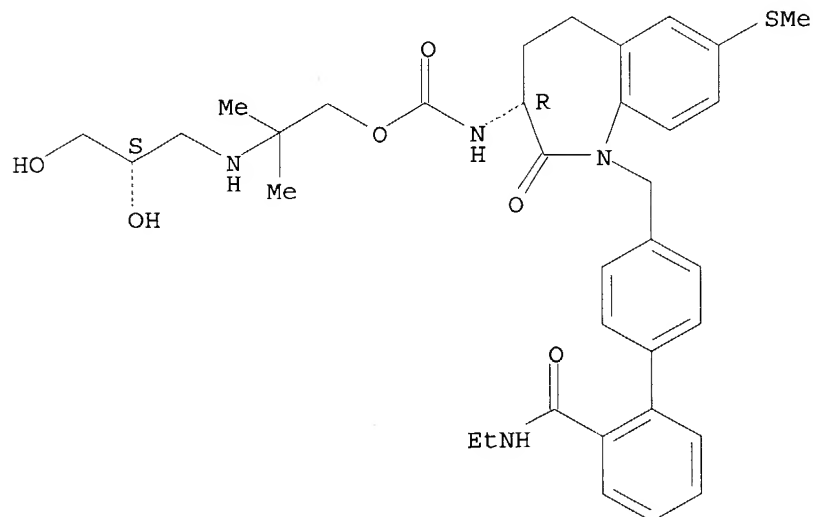
Absolute stereochemistry.



RN 169953-93-9 HCAPLUS

CN Carbamic acid, [1-[[2'-[(ethylamino)carbonyl][1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-2-oxo-1H-1-benzazepin-3-yl]-, 2-[(2,3-dihydroxypropyl)amino]-2-methylpropyl ester, [S-(R*,S*)]- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



L52 ANSWER 10 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:807968 HCAPLUS

DOCUMENT NUMBER: 123:228011

ENTRY DATE: Entered STN: 23 Sep 1995

TITLE: Preparation of N-(benzazepinonyl)alkanamides as growth hormone release promoters

INVENTOR(S): Bochis, Richard J.; Hodges, Paul J.; Schoen, William R.; Wyvratt, Matthew J., Jr.

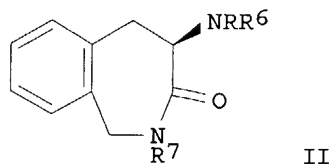
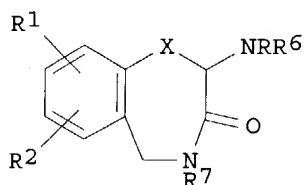
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
 SOURCE: PCT Int. Appl., 185 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 INT. PATENT CLASSIF.:
 MAIN: A61K031-55
 SECONDARY: C07D209-34; C07D215-227; C07D223-16
 CLASSIFICATION: 27-21 (Heterocyclic Compounds (One Hetero Atom))
 Section cross-reference(s): 1
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9509633	A1	19950413	WO 1994-US11086	19940930
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5545735	A	19960813	US 1993-132074	19931004
AU 9479616	A1	19950501	AU 1994-79616	19940930
PRIORITY APPLN. INFO.:			US 1993-132074	A 19931004
			WO 1994-US11086	W 19940930

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9509633	ICM	A61K031-55
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OTHER SOURCE(S):		MARPAT 123:228011

GRAPHIC IMAGE:



ABSTRACT:

Title compds. [I; R = COANR4R5; A = (CH₂)_xCR8R8a(CH₂)_y; R₁,R₂ = H, halo, (prefluoro)alkyl(oxy), etc.; R₄,R₅ = H, alk(en)yl, Ph, etc.; R₆ = H, alkyl, phenyl(alkyl); R₇ = (CH₂)_qLwR9; L = (un)substituted phenylene; R₈,R_{8a} = H, alkyl, CF₃, Ph, etc.; R₉ = (un)substituted Ph; X = CH₂, SO₀-2; q = 0-4; x,y = 0-3; w = 0 or 1] were prepared as growth hormone release promoters (no data). Thus, tert-Bu (2S,3R)-6-oxo-2,3-diphenylmorpholine-4-carboxylate was alkylated with 2-(NC)C₆H₄CH₂Br and the product treated with NaBH₄/Co(NO₃)₂ to give benzazepine II [R = (1R,2S)-(CHPh)₂OH, R₆ = CO₂CMe₃, R₇ = H] which was N-alkylated with 4-(BrH₂C)C₆H₄C₆H₄NO₂-2 (preparation given) and the product converted in 3 steps to II [R₇ = CH₂C₆H₄[C₆H₄(NHCONHMe)-4]-4] (III; R = R₆ = H). The latter was amidated by Me₃CO₂CNHCM₂CH₂CO₂H to give, after deprotection, III (R₇ = COCH₂CMe₂NH₂).

SUPPL. TERM: benzazepinonylalkanamide prepn growth hormone release promoter

INDEX TERM: Antiobesity agents
(preparation of N-(benzazepinonyl)alkanamides as growth hormone release promoters)

INDEX TERM: Osteoporosis
(treatment; preparation of N-(benzazepinonyl)alkanamides as growth hormone release promoters)

INDEX TERM: Animal metabolism
(disorder, catabolic, nitrogen wasting; preparation of N-(benzazepinonyl)alkanamides as growth hormone release promoters)

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 168058-77-3P 168058-78-4P 168058-79-5P 168058-80-8P
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 168058-93-3P 168058-94-4P 168058-95-5P 168058-96-6P
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 168059-13-0P 168059-14-1P 168059-15-2P 168059-16-3P
 168059-17-4P 168059-18-5P 168059-19-6P

ROLE: BAC (Biological activity or effector, except adverse);
 BSU (Biological study, unclassified); SPN (Synthetic
 preparation); THU (Therapeutic use); BIOL (Biological
 study); PREP (Preparation); USES (Uses)

(preparation of N-(benzazepinonyl)alkanamides as growth
 hormone release promoters)

INDEX TERM: 115-11-7, Isobutylene, reactions 577-19-5,
 2-Bromonitrobenzene 873-75-6, 4-Bromobenzyl alcohol
 3959-05-5, 2-Bromobenzylamine 5720-05-8, 4-Tolylboronic
 acid 22115-41-9, α -Bromo-o-toluenitrile
 24424-99-5, Di-tert-butyl dicarbonate 30992-29-1,
 N-(tert-Butoxycarbonyl)- α -methylalanine 112741-50-1

ROLE: RCT (Reactant); RACT (Reactant or reagent)

(preparation of N-(benzazepinonyl)alkanamides as growth
 hormone release promoters)

INDEX TERM: 4879-95-2P, 4,4-Dimethylazetidin-2-one 70680-21-6P,
 4-Methyl-2'-nitro-1,1'-biphenyl 114772-39-3P
 129765-95-3P, 3-(tert-Butoxycarbonylamino)-3-methylbutanoic
 acid 133776-42-8P, 4-Bromobenzyl tert-butyldimethylsilyl
 ether 147239-62-1P 148289-82-1P 155300-46-2P
 162356-90-3P, N-(tert-Butoxycarbonyl)-2-bromobenzylamine
 162356-92-5P 162356-93-6P 168056-98-2P 168059-20-9P
 168059-21-0P 168059-22-1P 168059-23-2P 168059-24-3P
 168059-25-4P 168059-26-5P 168059-27-6P 168059-28-7P
 168059-29-8P 168059-30-1P

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP
 (Preparation); RACT (Reactant or reagent)

(preparation of N-(benzazepinonyl)alkanamides as growth
 hormone release promoters)

INDEX TERM: 9002-72-6, Growth hormone
 ROLE: BPR (Biological process); BSU (Biological study,
 unclassified); BIOL (Biological study); PROC (Process)
 (release promoters; N-(benzazepinonyl)alkanamides)

IT 168057-13-4P 168057-14-5P 168057-15-6P
 168057-16-7P 168057-25-8P 168057-26-9P
 168057-27-0P 168057-37-2P 168057-45-2P
 168057-46-3P 168057-47-4P 168057-55-4P
 168057-61-2P 168057-67-8P 168057-69-0P
 168057-72-5P 168057-78-1P 168057-84-9P
 168057-88-3P 168057-92-9P 168057-96-3P
 168058-00-2P 168058-04-6P

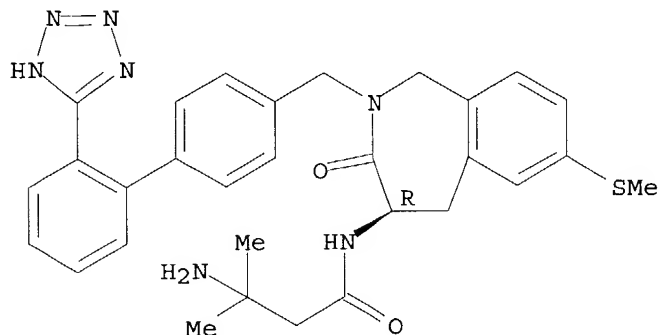
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
 BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of N-(benzazepinonyl)alkanamides as growth hormone release
 promoters)

RN 168057-13-4 HCAPLUS

CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-2-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

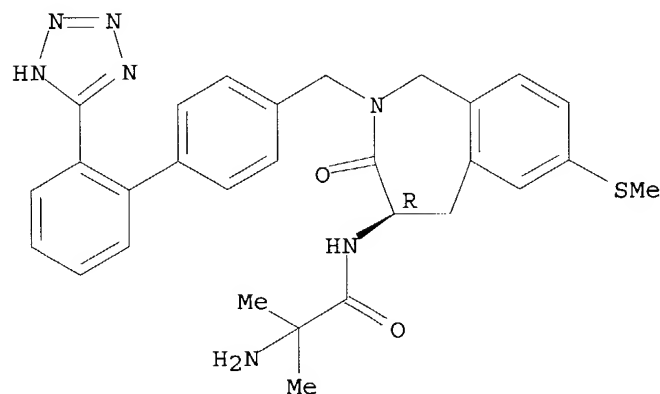
Absolute stereochemistry.



RN 168057-14-5 HCAPLUS

CN Propanamide, 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-2-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

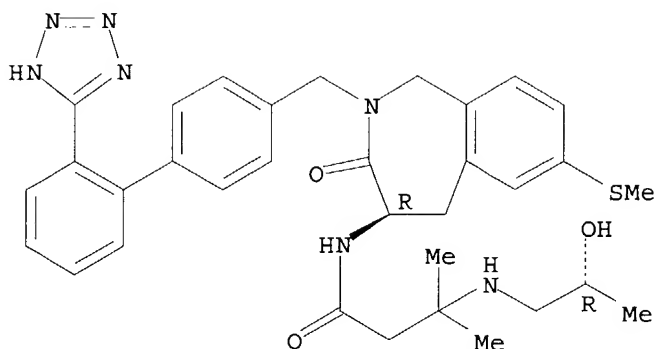
Absolute stereochemistry.



RN 168057-15-6 HCAPLUS

CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-2-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-2-benzazepin-4-yl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

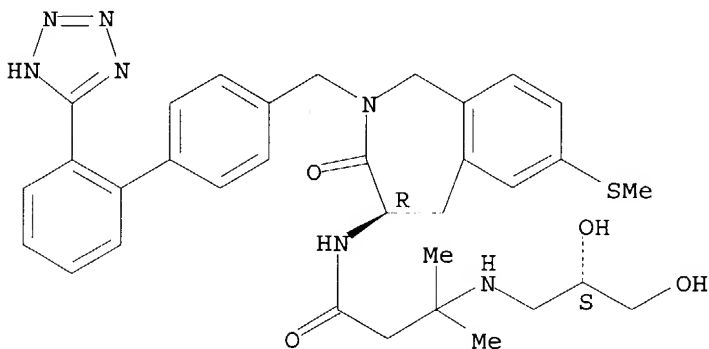
Absolute stereochemistry.



RN 168057-16-7 HCAPLUS

CN Butanamide, 3-[(2,3-dihydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-2-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-2-benzazepin-4-yl]-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

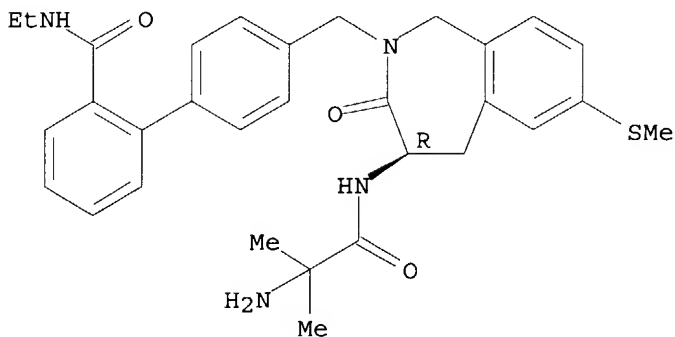
Absolute stereochemistry.



RN 168057-25-8 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxamide, 4'-[[4-[(2-amino-2-methyl-1-oxopropyl)amino]-1,3,4,5-tetrahydro-7-(methylthio)-3-oxo-2H-2-benzazepin-2-yl]methyl]-N-ethyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

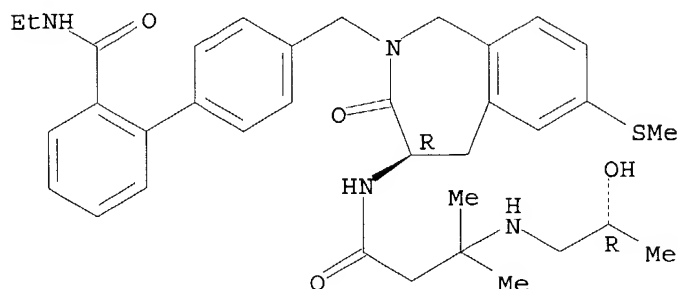


RN 168057-26-9 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxamide, N-ethyl-4'-[[1,3,4,5-tetrahydro-4-[[3-[(2-hydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-7-(methylthio)-3-oxo-2H-2-

benzazepin-2-yl)methyl]-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

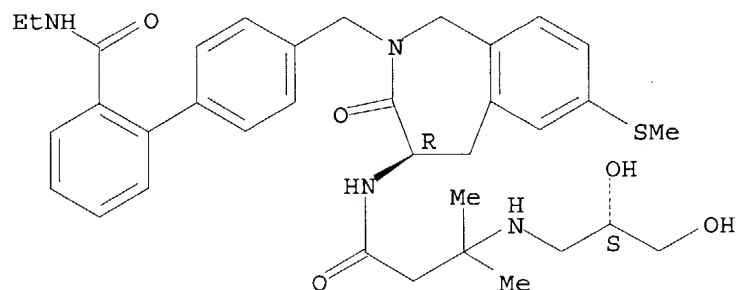
Absolute stereochemistry.



RN 168057-27-0 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxamide, 4'-[[4-[[3-[(2,3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-1,3,4,5-tetrahydro-7-(methylthio)-3-oxo-2H-2-benzazepin-2-yl)methyl]-N-ethyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

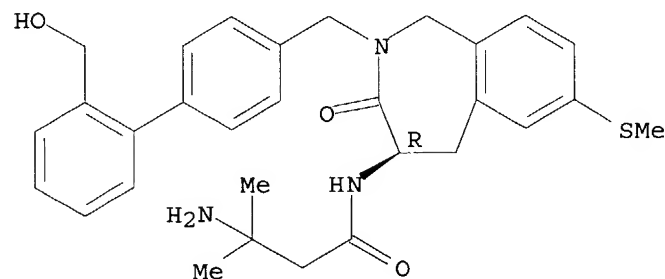
Absolute stereochemistry.



RN 168057-37-2 HCAPLUS

CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-(hydroxymethyl)[1,1'-biphenyl]-4-yl)methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

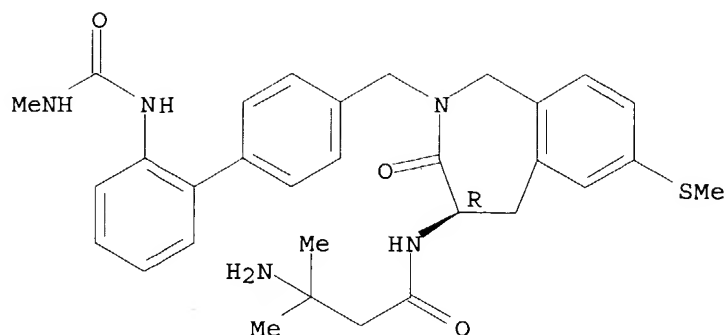
Absolute stereochemistry.



RN 168057-45-2 HCAPLUS

CN Butanamide, 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl)methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

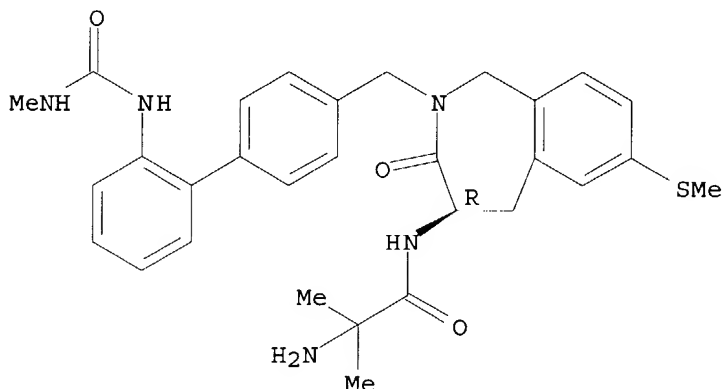
Absolute stereochemistry.



RN 168057-46-3 HCAPLUS

CN Propanamide, 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-[[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

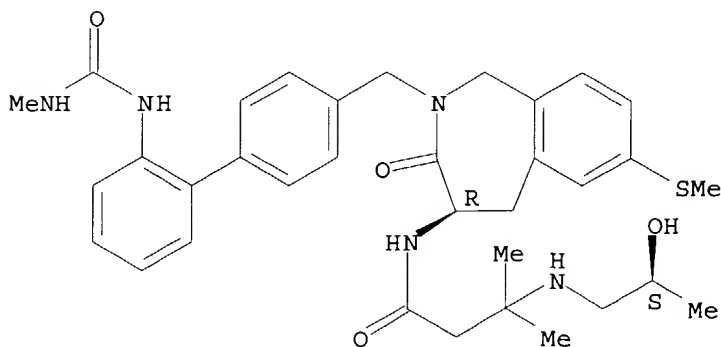
Absolute stereochemistry.



RN 168057-47-4 HCAPLUS

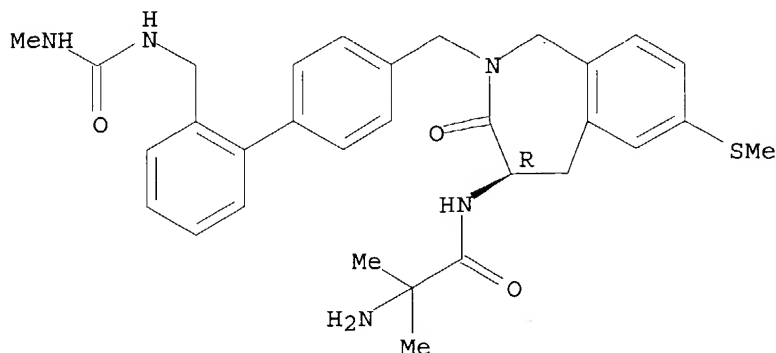
CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-[[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-7-(methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



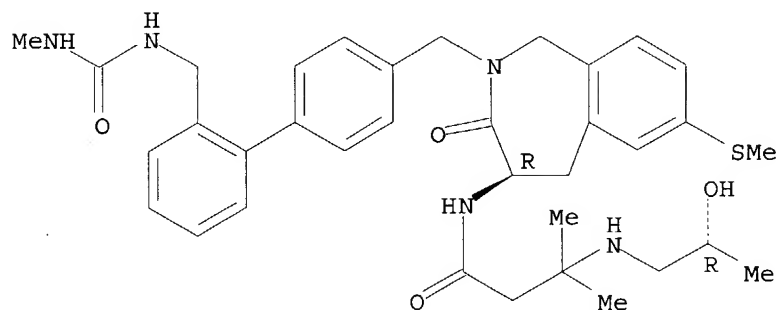
RN 168057-55-4 HCAPLUS
 CN Propanamide, 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-2-[[2'-
 [[[methylamino]carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-
 (methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 168057-61-2 HCAPLUS
 CN Butanamide, 3-[(2-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-
 [[2'-[[[methylamino]carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-7-
 (methylthio)-3-oxo-1H-2-benzazepin-4-yl]-, [R-(R*,R*)]- (9CI) (CA INDEX
 NAME)

Absolute stereochemistry.



RN 168057-67-8 HCAPLUS
 CN Propanamide, 2-amino-N-[2-[[2'-[[[aminocarbonyl]amino]methyl][1,1'-
 biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-7-(methylthio)-3-oxo-1H-2-
 benzazepin-4-yl]-2-methyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.